# Creating a BioDefense Industry: BioShield II

Testimony by
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Chairman Hatch, I am pleased to be here today continuing to work with you on these critical bioterrorism preparedness issues. You understand the urgency and complexity of these matters. There is no Member of the Senate who matches your expertise on biomedical research and development issues, intellectual property and liability protections, tax incentives for entrepreneurs, and FDA regulatory and bioethics issues. You have a powerhouse staff. I could not have a better, more influential and respected partner for the bills that we've introduced. Your leadership – exemplified by this hearing – is impressive and welcome.

Chairman Gregg, your leadership in enacting Project BioShield was exceptional. You demonstrated a real command of the complex issues we face in engaging the biopharma company as part of our national defense infrastructure. You have a powerhouse staff as well.

Senator Kennedy, you have been a leader on public health issues for many decades. The many prominent biotech companies in Massachusetts view you as champion who understands their issues. Your staff has always been considered to be one of the best on the Hill.

Senator Leahy, you and your staff were targets of the October anthrax attack. Fortunately, the letter was intercepted before it reached your office, making this a personal issue for you and your staff. You understand the threat posed by these pathogens.

Working together, there is nothing the four of us can't accomplish in terms of bioterrorism preparedness. Enacting BioShield II should be our next step.

## 10/15 – Bioterrorism's 9/11

None of us on the Hill – especially those of us with offices in the Hart Building – will forget October 15, the date of the anthrax attack on Senator Daschle's office. This date is the bioterrorism equivalent of September 11. We also need to remember October 5, the third anniversary of the 2001 anthrax death of Bob Stevens, a photo editor at American Media in Boca Raton, Florida, and November 17, the third anniversary of the discovery of a similar anthrax laced letter mailed to Senator Leahy. Similar anthrax attacks during these weeks were directed at NBC, ABC, CBS and other news organizations. All told five people died and thousands who might have been exposed were put on Cipro, including many of us and many of our staff.

This attack on civilians with weapons grade anthrax was unprovoked. And unlike the case with the 9/11 attacks, we still don't know who mailed the anthrax letters. As with the 9/11 attacks, we were totally unprepared for the anthrax-laced letters. We are responding forcefully to the 9/11 attacks – the commission that Senator McCain and I proposed has issued a superb report and the Government Affairs Committee, where I serve as the Ranking Democrat, is hard at work translating its recommendations into legislation. Unfortunately our response to the 10/15 anthrax attack has not been as forceful.

Unlike our response to 9/11, we have not seemed to consider the 10/15 attack to be the equivalent of a declaration of war. While we have taken a few constructive steps to strengthen our Bioterror defenses, we remain painfully vulnerable to another Bioterror attack, or a chemical or radiological attack.

## Timeliness of Hearings

The issue in this hearing could not be more timely: Have we done enough in enacting BioShield to ensure that we will secure the development of the medical countermeasures we need in the event of an attack, what metrics are we applying to determine whether BioShield is sufficient, and, in the event that BioShield does not accomplish enough, what policy options exist for strengthening our effort with BioShield II.

It is not too early to ask these questions; this is urgent and long-term research. It often takes ten or more years to bring a new therapeutic to market and some of the research – particularly on new antivirals – may take many more than ten years. Stocks of bioweapons developed by the former Soviet Union might fall into the hands of terrorists. We know that terrorist groups are intensely interested in acquiring Bioterror weapons and they will have no compunctions about using them.

We can't wait several years to determine if BioShield is sufficient. We need to set clear metrics of its impact and take decisive action to move to enact BioShield II if that proves to be necessary.

Many of us believe that BioShield is a step in the right direction, but we don't believe that BioShield is sufficient. If we listen carefully, we will hear that the biopharma industry — which is hiding on this issue — is saying that BioShield is not enough. So we already have strong warning signs that more needs to be done. And Senator Hatch and I – and hopefully Senator Gregg and Kennedy – will shortly be introducing BioShield II, a bill to set the terms of the debate just as our earlier bill served as the source for BioShield. This hearing starts the process for considering these additional legislative measures.

# Nature of the Bioterror Threat

There is no terror threat greater than that of Bioterror. With an attack with a plane, a chemical attack or a radiological dispersion device (a dirty bomb), the loss of life can be catastrophic, but the perimeter of the attack is fixed. With an infectious disease, the perimeter of an attack might grow exponentially as the infection spreads. It is possible to kill thousands with a bomb, chemical or radiation, but it is possible to kill millions with a Bioterror pathogen.

In the 2001 anthrax attack, the terrorist wrote a note in the letter to Senator Daschle that said, "09-11-01. You can not stop us. We have this anthrax. You die now. Are you afraid? Death to America. Death to Israel. Allah is great." If this note had not been included in the letter, and if the intern who opened the letter hadn't been suspicious, it is possible that some Senators and many Capitol Hill staff from our offices — perhaps hundreds — might have died. We would only have discovered the attack in hospital emergency rooms, where Cipro might have proven to be ineffective. Cipro works as a prophylaxis only when it catches anthrax early, before the toxins are released into the bloodstream, which can happen within 24 hours of an infection. Our current anthrax vaccine is administered in six shots over 18 months.

The 9/11 Commission report states that al Qaeda "was making advances in its ability to product anthrax prior to Sept. 11" and cited former CIA Director George Tenet as warning that an anthrax attack is "one of the most immediate threats the U.S. is likely to face." Russia developed dozens of strains of anthrax and the security at these former bioweapons laboratories is suspect. It is estimated that a mason jar of anthrax spores sprayed over an urban area could infect 400,000 residents, and if undetected until they started showing up in emergency rooms, kill half of them. It is also estimated that one hundred anthrax laced letters could cross contaminate thirty million letters and infect 10,000 people with anthrax. Imagine what would happen if our mail system – which processed over 200 billion pieces of mail last year – were closed for a few months. What we need, and don't yet have, is a therapeutic that disarms the anthrax toxins at a late stage of the disease — which is the aim of a pending RFP at the Department of Health and Human Services (see below).

We saw the potential for morbidity and mortality, and massive economic disruption, with SARS. When SARS was rampant, Beijing, Hong Kong and Shanghai closed down. Quarantines were imposed and China authorized the death penalty on anyone who willfully spread the disease. During the epidemic, there were reports that the SARS virus was mutating to become more virulent. In China's countryside, fear of SARS has led to some villages setting up roadblocks to keep away people from Beijing and at least four riots against quarantine centers have been reported in recent days. Thousands were quarantined in China. In the end SARS spread to thirty countries on five continents, sickening nearly 9,000 and killing 850. SARS is a zoonotic disease that apparently can jump back and forth between animals and man, which makes it much more difficult to eradicate it. We may not have seen the last of it.

We can also remember the devastating impact of the 1918 Spanish flu pandemic that killed more than died in the first World War, about 30-40 million people (equivalent to 100 million today). In the month of October, 1918, 200,000 Americans died of the disease, 43,000 soldiers died, and 28% of our population was infected. The flu's lethality rate was only 2.5%; the lethality rate of the most common form of smallpox, variola major, is 30% and for hemorrhagic smallpox it approaches 100%. The lethality rate for SARS was about 15%. If the 1918 flu pandemic killed the equivalent of 100 million people, think of how many smallpox or SARS — both of which could be weaponized by terrorists — could kill.

Public health authorities are concerned about the incidence of avian influenza in humans. There is now concrete evidence that this virus can be transmitted human-to-human.[1] When humans contract the pathogen from birds, the death rates are very high; a majority die. Since January 2004, a total of 23 confirmed human cases of avian influenza A (H5N1) virus infections have been reported in Vietnam with 19 deaths and 12 cases in Thailand with 9 deaths. These cases were associated with widespread H5N1 poultry outbreaks that occurred at commercial and small backyard poultry farms. Since December 2003, nine countries have reported H5N1 outbreaks among poultry. More than 100 million chickens have been culled in an effort to stop the outbreak. The virus now appears to be able to infect mammalian hosts, including pigs and cats, an unusual prowess for an avian virus. This raises concern as pigs are also hosts of human flu viruses and this could yield a hybrid avian flu strain that can be passed human-to-human. The avian flu virus apparently is now carried by migratory birds so it may be very difficult to eradicate the virus.[2] We have no vaccine for the disease and the one therapeutic — Tamiflu — is only effective if given very early after the onset of symptoms. It is feared that the virus might evolve resistance to Tamiflu. Public health officials believe that in theory the avian flu could cause a "pandemic killing millions of people worldwide, and possibly hundreds of millions."[3] Whether H5N1 could be used as a Bioterror weapon against agriculture or humans is not known.

In 1947 there was an outbreak of smallpox in New York City. Eventually two of the twelve who were infected died. But the smallpox vaccination campaign was massive — 500,000 New Yorkers received smallpox vaccinations the first day and eventually 6.35 million were vaccinated in less than a month, 85% of the city's population. . President Truman was vaccinated prior to a trip to New York City.

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[1] A case in Thailand might be confirmed as the first human-to-human transmission of the virus. See Keith Bradsher, "Experts Confront Major Obstacles in Containing Violent Bird Flu," New York Times, September 30, 2004 at A-1.

[2] "Lethal Bird Flu Reemerges in Four East Asian Countries," Washington Post, September 15, 2004 at A21.

[3] See "Thais Suspect," Footnote 3. Bradsher states, "Many scientists think that an avian influenza strain that jumped to people was responsible for the Spanish influenza of 1918 and 1919, which is believed to have killed anywhere from 20 million to 100 million people t a time when the world had a quarter of its current population."

If we suffered another smallpox outbreak, it is not likely that a vaccination campaign would go so smoothly. It is now estimated that if the current smallpox vaccine were deployed in the United States 350 to 500 individuals might die from complications. The current vaccine is not recommended for patients who have eczema or are immunosuppressed, HIV-positive or are pregnant. Even worse, based on a 1971 accidental release of smallpox from a Soviet bioweapons laboratory, some speculate that the Soviets successfully weaponized a rare and especially lethal form of smallpox, hemorrhagic smallpox (with near 100% lethality).[4]

Mother Nature's pathogens are dangerous – smallpox, anthrax, plague, tularemia, glanders, typhus, Q fever, Venezuelan equine encephalitis, brucellosis, botulinum toxin, dengue fever, Lassa fever, Russian spring-summer encephalitis, Marburg, Ebola, Bolivian hemorrhagic fever, Argentinean hemorrhagic fever and fifty other pathogens could kill thousands or even millions. But on the horizon are more exotic and deadly pathogens.

We have reports that the Soviet Union developed genetically modified pathogens such as a hybrid plague producing diphtheria toxin. This manipulation increased virulence and made the plague microbe more resistant to vaccine. Other possibilities include a Venezuelan Equine Encephalomyelitis-plague hybrid is a combination of the virus and the bacteria; we have no idea what symptoms such a pathogen would manifest or how we might diagnose or treat it. Other hybrid pathogens might be developed, including a Venezuelan Equine Encephalomyelitis-Ebola hybrid.

We have reports that the Soviet Union developed a powdered form of Marburg (a hemorrhagic fever where every cell and organ of the victim bleeds). Symptoms of Marburg include kidney failure, recurrent hepatitis, inflammation of the spinal cord, bone marrow, eyes, testes, and parotid gland, hemorrhaging into the skin, mucous membranes, internal organs, stomach, and intestines, swelling of the spleen, lymph nodes, kidneys, pancreas, and brain, convulsions, coma and amnesia.

Genetically modified pathogens are another possibility. In 2001 the Journal of Virology[5] reported that Australian scientists seeking to create a contraceptive for mice used recombinant DNA technology to introduce Interleukin 4 into mouse pox and found that it created an especially virulent virus. In the words of the scientists, "These data

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[4] See Dr. Alan Zelicoff's chapter "An Epidemiological Analysis of the 1971 Smallpox Outbreak in Aralsk, Kazakhstan," in Occasional Paper No. 9, *The 1971 Smallpox Epidemic in Aralsk, Kazakhstan, and the Soviet Biological Warfare Program*, edited by Jonathan B. Tucker and Raymond A. Zilinskas, June 2002 and CNS response by Dr. Serguei Popov, former Soviet bioweapons researcher, where he states, "In particular, there was a high interest in creating strains of hemorrhagic smallpox virus using the new methods of molecular biology."

[5] Jackson RJ, Ramsey AJ, Christensen DC, et. al. "Expression of Mouse Interleukin-4 by a Recombinant Ectromelia Virus Suppresses Cytotytic Lymphocyte Responses and Overcomes Genetic Resistance to Mousepox," Journal of Virology 2001: 75: 1205-10.

therefore suggest that virus-encoded IL-4 not only suppresses primary antiviral cell-mediated immune responses but also can inhibit the expression of immune memory responses." This public research suggests that introducing IL-4 can create an Andromeda stain of a virus, information of potential use to terrorist sociopaths. In addition, published studies describe how to create a recombinant vaccina virus to induce allergic encephalomyelitis in rabbits (and potentially - highly lethal smallpox virus capable of causing paralyses in humans) and how to synthesize the polio virus in a biochemical laboratory.

Other possible pathogens – some of which the Soviet worked on[6] – include antibiotic resistant pathogens. The Soviets apparently developed a strain of plague resistant to ten different antibiotics, and a strain of anthrax resistant to seven different antibiotics. Some claim the Soviets developed a strain of anthrax resistant to the current U.S. anthrax vaccine. A part of this research in a hamster model was published in Vaccine, so this information is available to terrorists.[7]

Other exotic pathogens might include autoimmune peptides, antibiotic induced toxins, and bioregulators and biomodulators. An autoimmune peptide might stimulate an autoimmune attack against the myelin that sheaths the target's nerve cells.[8] Antibiotic induced toxins are hybrid bacteria-viruses where antibiotics administered to treat the bacterial infection stimulate the virus to release a deadly toxin; the greater the doses of antibiotics, the more toxins are released. Bioregulators and biomodulators are synthetic chemical that bond to and disrupt receptors that govern critical functions of the target, including nerve, retinal, liver, kidney, heart, or muscle cells to cause paralysis, blindness, schizophrenia, coma, or memory loss.[9]

Some of these might be available now from the 60 bioterror research laboratories maintained by the Soviet Union. Eventually, terrorists might be able to set up full-blown

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[6] See November 1, 2000 interview of Serguei Popov, former Soviet bioweapons researcher to the Journal of Homeland Security in the appendix.

[7] See Pomerantsev AP, Staritsin NA, Mockov YuV, Marinin LI., Expression of cereolysine AB genes in Bacillus anthracis vaccine strain ensures protection against experimental hemolytic anthrax infection. Vaccine (Dec. 1997 Dec; 17-18 and 1846-50.

[8] See "A Virus-Induced Molecular Mimicry Model of Multiple Sclerosis," which shows that a naturally infectious virus encoding a myelin epitote mimic can directly initiate organ specific T-cell mediated autoimmunity – a line of research the Russians were pursuing more than ten years ago. Olson JK, Croxford JL, Calenoff MA, Dal Canto MC, Miller SD, J Clin Invest, July 2001, Volume 108, Number 2, 311-318.

[9] See "The Looming Threat: Bioweapons are much more prevalent and virulent than most of us realize. And we have little defense," Mark Williams, Acumen, Volume 1, Number IV. Some of the examples of this research were published in the Soviet scientific literature. See Borzenkov VM, Pomerantsev AP, Pomerantseva OM, Ashmarin IP., Study of nonpathogenic strains of francisella, brucella and yersinia as producers of recombinant beta-endorphin [Article in Russian], Bull Eksp Biol Med. (June 1994; 117(6) at 612-5).

biotechnology laboratories. Rogue states could do so and they might then transfer bioweapons to terrorists or lose control of them. Over the long term, as the power of modern biotechnology grows, the Bioterror threat will grow and increasingly virulent and exotic weapons might become threats.

In November 2003 the CIA's Office of Transnational Issues published "Our Darker Bioweapons Future," which stated that the effect of bioengineered weapons "could be worse than any disease known to man." The rapid evolution of biotechnology makes monitoring development of bioweapons extremely difficult. Some of these weapons might enable the development of "a class of new, more virulent biological agents engineered to attack distinct biochemical pathways and elicit specific effects, claimed panel members. The same science that may cure some of our worst diseases could be used to create the world's most frightening weapons." It specifically mentioned the possibility of "binary BW agents that only become effective when two components are combined (a particularly insidious example would be a mild pathogen that when combined with its antidote becomes virulent)"; "designer" BW agents created to be antibiotic resistant or to evade an immune response; weaponized gene therapy vectors that effect permanent change in the victim's genetic makeup; or a "stealth" virus, which could lie dormant inside the victim for an extended period *before* being triggered.

Illustrating the speed with which biotechnology is advancing to create new bioterrorism threats is a recent announcement by Craig Venter and his Institute for Biological Energy Alternatives that in fourteen days they had synthetically created working copies of the known existing bacteriophage virus Phi X174. Other researchers had previously synthesized the poliovirus, which is slightly bigger, employing enzymes usually found in cells. But this effort took years to achieve and produced viruses with defects in their code. So the timescale has shifted from years to weeks to make a virus. There are other bigger viruses that would require more time to assemble. Venter asserts that his team could make a bacteria with about 60 times larger genome from scratch within about a year of starting. Does this mean that the debate about whether to destroy smallpox virus stocks is pointless because any virus or bacteria whose DNA sequence is published is eventually going to be easily creatable by labs all around the world?

These pathogens might be deployed by terrorists, sociopaths or rogue states that have no compunctions about killing massive numbers of "infidels" or enemies in the West. They would be experience great joy in sowing widespread panic, injury and death in America. Osama Bin Laden's spokesman, Sulaiman Abu Ghaith, bragged that al Qaeda has "the right to kill 4 million Americans" in response to deaths he claims the west has inflicted on Muslims. We are facing sociopaths with no compunction about using whatever weapons of mass destruction they can develop or secure. They would see the potential to unleash a weapon in North America and trust that our borders would be closed so that it would only rage here and not spread to the Muslim world.[10]

[10] All of the incentives we've proposed in our bills go to the development of medical countermeasures to weapons of mass destruction, including biological nuclear /radiological and chemical agents. While everyone is surely aware of biological

## Economic Consequences of an Attack

The Brookings Institution estimated that a Bioterror attack would cause one million casualties and inflict $750 billion in economic damage. An earlier Office of Technology Assessment found that there might be three million casualties. If there are this many casualties, what can we expect in the way of public panic and flight? A 2004 poll finds that "most Americans would not cooperate as officials would expect them to during a terrorism incident."[11] Only 2/5 said that they'd "follow instructions to go to a public vaccination site in a smallpox outbreak" and only 3/5 would "stay in a building other than their own home…" A vivid vision of what an attack might look like is found in Albert Camus' The Plague, with its incinerators and quarantine camps. We can review the history of the Black Death, which killed up to one of half of Europe's population between 1348 and 1349.

Imagine what would happen if the attack involves a pathogen for which we have no diagnostic, vaccine or therapeutic. If we resorted to quarantines, what would the rules of engagement be for the police and military forces we deploy to enforce it? Would it be possible to establish an effective quarantine if there is mass panic and flight? Would our hospitals be overwhelmed by the "worried well"? Would public health workers continue to serve or also flee? If our hospitals are contaminated, where would Americans receive medical care for non-terror related emergencies?

What would happen if a Bioterror, chemical or radiological attack closed Atlanta's Hartsfield International Airport – which handled nearly eighty million passengers last year? Or what would happen if we put a hold on the one hundred and twenty million international airline arrivals and departures we see each year? What would happen if we were forced to close our borders with Mexico and Canada – with 500 million crossings last year? What would happen if we restrained the 2.79 trillion automobile passenger miles driven in the U.S., one billion of which exceeded 100 miles?

What would happen if a terror attack rendered certain types of business activity uninsurable? What will happen if large swaths of residential real estate – none of which is currently insured for acts of terror – were contaminated and rendered worthless with anthrax spores?

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countermeasures like smallpox vaccine, it is somewhat misleading to call this legislation "BioShield." We also need to develop drugs and other countermeasures to radiation and chemical exposure. In point of fact, there are a number of such countermeasures now in advanced stages of development, including at least one compound that rebuilds bone marrow destroyed by exposure to radiation. We need to be sure to apply these incentives to all of these medicines, not just medicines to prepare us for a Bioterror attack.

[11] "Most in U.S. Don't Trust Government in Attack," Washington Post, September 15, 2004 at A16.

## Near Total Lack of Medicines

We are vulnerable to a Bioterror attack in many ways, but one of the most troubling is that we have essentially none of the diagnostics, therapeutics and vaccines we need to treat those who might be exposed or infected. If we don't have these medicines, we are likely to see quarantines and panic, which will amplify the damage and disruption. My office is on the 7th floor of the Hart Building, immediately above Senator Daschle's office. We were told if we immediately started a course of treatment with Cipro we would not die, so there was no panic. Think what would have happened if the government had said, "We don't know what this is, it's deadly, we have no way to tell who has been exposed, and we have no medicines to give you."

In the summer of 2000 the Defense Science Board found that we had only one of the fifty-seven diagnostics, drugs and vaccines we most need to respond to a Bioterror attack (we had a therapeutic for Chlamydia pittance, a bacteria). It projected that we'd have twenty of the fifty-seven within five years and thirty-four within twenty years. But today we have only two of the fifty-seven countermeasures (we now have a diagnostic for anthrax).[12]

At this rate of developing these medical countermeasures, we won't have twenty of them available until 2076 and we won't have thirty-four until 2132. This list does not include antibiotic resistant pathogens, hybrid pathogens, genetically modified pathogens, and a host of other exotic Bioterror pathogens.

## Little Sense of Urgency

The Congress and Administration have not responded to the anthrax attack with an appropriate sense of urgency, especially with regard to the development of medicines. We have not responded with a crash industrial development program as we did when we

[12] The DSB "stoplight chart" – The Projected Evolution of Diagnostics, Vaccines, and Therapeutics Against Major Bioagents with Strategic R&D and Supply Actions – gives a "green" light for diagnostics where there is a "treatment available," a "yellow" light where "treatments available.Production and/or use limitations" and a "red" light where there is "no approved treatment." For a diagnostic a "green" light is given for "diagnosis < 12 hours, no confirmatory testing, asymptomatic detection," a "yellow" light for "diagnosis 12-24 hours, may require confirmatory testing, some asymptomatic detection," and a "red" light for "diagnosis in more than 24 hours, require confirmatory testing, must be symptomatic." For vaccines, the DSB gives a "green" light to "generally available," a "yellow" light if "vaccine available, production and/or use limitations," and a "red" light for "vaccine not available." This scheme explains why the DSB gives a "yellow/red" light to the current smallpox and anthrax vaccines. It gives a "red" light for diagnostics, vaccines and therapeutics for plague, Burholderia mallei, B. pseudomallei, and clostridium perfingens. It gives two red lights for tularemia, brucellosis, salmonella, eastern equine encephalitis, and Venezuelan equine encephalitis.

developed radar during the Second World War or as we are now undoubtedly undertaking to detect roadside bombs. Reluctantly, I would characterize our national response as lackadaisical.

December 4 is the third anniversary of my introduction of legislation to provide incentives for the development of medical countermeasures – including diagnostics, therapeutics and vaccines — for Bioterror pathogens (S. 1764). Chairman Hatch, October 17 is the second anniversary of our introducing our first bill together on this subject (S. 3148) and we introduced our current bill on March 19 of last year (S. 666). Twenty months ago President Bush proposed Project BioShield, a bill based on one of the twelve titles in our bills, and it was finally enacted into law on July 21. If we enact one of the titles of our bill every two years, it'll take 22 more years to complete our legislative work.

The critical issue for this hearing is whether Project BioShield, Public Law, Public Law 108-276, is sufficient or whether we need to supplement it with BioShield II, a bill that you and I intend to introduce this fall. BioShield is only one title of our proposal – the title that provides that the government will define the size and terms of the market for a Bioterror countermeasure in advance before a biopharma companies puts its own capital at risk. This is a necessary first step; companies won't risk their capital to develop a product unless they can assess the possible rate of return (product sales) on their investment.

Enacting BioShield is a step in the right direction. If we were to enact only one idea first, this is the right first step. We will now see how the Department of Health and Human Services implements this law. We will see what R&D priorities it sets, whether it projects a market for these products sufficiently large to engage the better biopharma companies in this research, and whether it sets contract terms that company Chief Financial Officers find acceptable.

Unfortunately, we all heard a deafening silence from biopharma industry — the target of this legislation — as BioShield was being considered. The industry did essentially nothing to fix the Administration's draft – which the industry privately stated was laced with dysfunctional provisions. The industry did essentially nothing to pass BioShield. And the industry has said essentially nothing since BioShield was enacted.

It is clear to me that BioShield is not sufficient to secure development of the medical countermeasures we need, indeed, I believe it is woefully insufficient.

## Basis for Industry Skepticism

The industry is skeptical that the government will be a reliable partner during the development of Bioterror countermeasures. The basis of its skepticism runs deep.

The industry points to the Cipro procurement as a case in point. In 1999, before the anthrax attack, Bayer, the developer of Cipro, was asked by FDA and CDC to secure a label indication for Cipro for anthrax. The government wanted to have one antibiotic available that was explicitly labeled for anthrax – it understands that patients might be reluctant to take a medicine for anthrax where it is not labeled for this indication. Bayer incurred the expenses to do this with no expectation of ever utilizing the product in this manner, and when the attack occurred, Cipro was the only therapeutic with a label indication for anthrax. Bayer handled this emergency with honor. It immediately donated huge stocks of Cipro, 2 million tablets to the Postal Service and 2 million tablets to the Federal government to be used to protect those who might have been exposed or infected. The government then sought to procure additional stocks of Cipro and demanded that Bayer sell it as one-fourth the market price. Threats were made by Members of Congress that if Bayer would not agree to this price the government might step in to challenge the patent for Cipro. Bayer readily agreed to the deep discount. We can assume that every other purchaser of Cipro then demanded this same price and that this cut Bayer's market return for Cipro. To add insult to injury, Bayer has had to defend itself from lawsuits by those who took Cipro in response to the attack even though it did what was asked, provided more than enough free product to treat all patients and greatly reduced it's stockpile pricing. Bayer also was deeply concerned with employee and plant security risks when it was publicly identified as the sole source of this counter-bioterrorism agent.

The industry view this incident as proving that with regard to bioterrorism research, no good deed will go unpunished. If a large pharmaceutical company can be manhandled this way, what would happen to a small biotechnology company? The industry expects that if there is an attack, and the company has the indispensable medicine we need to respond to it, the government is likely to steal the product. The industry is deeply skeptical of the government already. It has very complex and often contentious relationships with other HHS agencies, including the Center for Medicare Services, the Food and Drug Administration, and the National Institute of Health. It has constant battles with state Medicaid agencies. This is not an industry that trusts government.

Some in Congress have proposed legislation that feed industry fears. In 1994 and 1995 legislation was introduced in the House (H.R.4370, introduced on May 10, 1994, and H.R.761, introduced on January 31, 1995) that provided the government with eminent domain power with regard to AIDS to confiscate "all potential curatives and all data…regarding their development," including the patents for such compounds. Similarly, in 1999 and 2001 legislation was introduced in the House (H.R.2927, introduced on September 23, 1999, and H.R.1708, introduced on May 3, 2001) that provided for the compulsory licensing of "any subject invention related to health" where the government finds it "necessary to alleviate health or safety needs" or the patented

material is "priced higher than may be reasonably expected based on criteria developed by the Secretary of Commerce." Legislation has been introduced that would deny the benefits of the R&D tax credit for research by pharmaceutical companies where the products that arise from that research are sold at higher prices abroad than in the United States. See H.R.3665 introduced on February 15, 2000.

The industry response to these threats to its patents must be seen in light of the events of March 14, 2000. On that day a White House spokesman apparently indicated that the government might move to challenge some biopharma industry patents for genes. The industry lost $40 billion in market capitalization in the panic that ensued on Wall Street. That was not only the beginning of a deep drought in biotech company financing, it was the beginning of the collapse of the entire NASDAQ market. A similar collapse and drought had occurred in 1993-1994 the Clinton Administration proposed that the prices of "breakthrough drugs would be reviewed by a special government panel.

The issue of price controls and patents was recently considered and rejected by NIH in response to a petition for the government to march-in on the patent of Abbott Laboratories for ritonavir (sold under the name of Norvir), an AIDS therapeutic. The petitioner, Essential Inventions, asked that the government cancel the license of this patent to Abbott, which it alleged was charging too much for Norvir. The petitioner had also been involved in the 1994-1995 NIH proceeding, where NIH reviewed the impact of its 1989 protocol to review whether "reasonable" prices were being charged by companies that had licenses with NIH. NIH found that this price review process was destroying the NIH technology transfer program – companies simply would not enter into agreements with NIH. As a result, NIH repealed the price review process. The new march-in petition raised essentially the same issues and if the petition had been granted, we could have expected that the NIH tech transfer process will be crippled – again, as it was from 1989-1995. In rejecting the petition, NIH did not state, however, that is has no right to march-in based on the price of a product, implying that it could or might assert such power in the future. This can only have a chilling impact on companies considering entering into biodefense procurement and research agreements.

Aside from fears about government actions, we could not have picked a worse time to ask the industry to undertake a whole new portfolio of research. The biotech NASDAQ index stood at 1380 and it now stands at about 725. The Amex biotech indexed peaked at 801 and it now stands at about 525. The Dow Jones pharmaceutical index peaked at 420 and it now stands at about 275. The biotech industry raised $32 billion in capital in 2000 and only $16 billion last year. In June of this year, 36% of the public biotech companies had stock trading at less than $5 per share. There were 67 biotech IPOs in 2000 and only 7 last year. The industry losses each year continue to run to $4 billion. The National Venture Capital Association reports that only 2% of venture money went into biodefense following the October anthrax attack.

Of the 506 drugs publicly disclosed to be under development by the 22 largest pharmaceutical companies, only 32 are for infectious disease and half of these are aimed

at HIV/AIDS. In 1967 we had 67 vaccine companies and in 2002 we had 12. World wide sales vaccines is about $6 billion, but the world wide sales of Lipitor are $10 billion.

In addition, it is not clear whether the government is able or willing to provide the industry with the operating margins – profits – it sees for its other products.[13] The operating margin for successful biopharma companies is 2.76 to 3.74 times as great as the operating margins for major defense contractors. This means that the defense contractor model will not work to engage biopharma companies in developing medical countermeasures for bioterror agents. Whether the successful bipharma companies are "too profitable" is a separate issue. The issue addressed here is the operating margin that successful biopharma companies seek and expect as they assess lines of research to undertake. If the operating margin for biodefense research is less, or substantially less than the operating margin for non-biodefense research, it is not likely that these companies will choose to undertake biodefense research. This research is a voluntary undertaking putting their capital at risk; there is no requirement that they do this when the prospects for profits are not competitive with that from other lines of research.

Mostly we are seeing the industry hiding, not commenting on the pending legislation, not participating in the legislative process, and making every effort not to seem to be unpatriotic or greedy. Companies do not say in public that they are disinterested. They will not say what package of incentives would be sufficient to persuade them to take up biodefense work. They fear a debate on patents. They feel besieged by the current drug import debate, pressure from CMS over drug prices, and the debate over generic biologics. While I understand these fears, we simply have to know what it would take in the way of incentives to establish a biodefense industry. If the incentives in BioShield or BioShield II are not sufficient, we need to know what incentives are sufficient. We need to know what reassurances would persuade the industry that what happened to Bayer will never happen again. And only the industry can give us a clear answer to these questions. We cannot have a dialogue on these urgent national questions without the government listening and the industry speaking.

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[13] The operating margin for the major defense contractors was 8.5% in 2001 and 9.5% in 2002. The operating margin for the successful biotechnology companies listed was 31.8% in 2001 and 28% in 2002. This operating margin is 3.74 times and 2.91 times as great for 2001 and 2002 respectively as the operating margin for the major defense contractors. The operating margin for the successful pharmaceutical companies was 29.5% in 2001 and 26.5% in 2002. This operating margin is 3.47 and 2.76 times as great for 2001 and 2002 respectively as the operating margin for the defense contractors. Operating margin is profit before tax. The operating margin for the defense contractors has been adjusted for good will. Operating margin is calculated by dividing a company's operating profit by net sales. It is also known as operating profit margin or net profit margin. Operating profit it typically assessed before taking into account interest and taxes. Source: Compiled from publicly available information with assistance from Michael King, Banc of America Securities LLC.

# Shifting Risk to the Industry

The goal of BioShield II is to shift the risk of countermeasure research and development to the industry. Given the skepticism of the industry about the reliability of the government as a partner, shifting the risk to the industry — with it risking its own capital to fund the R&D — will be difficult. But engaging the industry as entrepreneurs, rather than as defense contractors, is likely to be less expensive for the government and it's much more likely to secure the development of the medicines that we need.

If the government funds the research, the industry can expect to receive the operating margins that are typically paid to defense contractors – 8.5-9.5%. If the industry risks its own capital and funds the failures and cost overruns, the industry believes it would be justified demanding the operating margins that are typically paid in the commercial sector – 28-32%.

If the government funds the research, the industry expects that the government will control or own the patents associated with the medicines. If the industry funds the research, it believes it has claims on all the patents.

The only companies that are likely to accept a defense contractor model are companies with no approved products, no revenue from product sales, and no other source of capital to keep the lights on. For them government funding is "non-dilution" capital, meaning it's a form of capital that does not dilute the ownership shares of its current shareholders. Many biotech companies have stock trading in the low single digits, so they cannot issue another round of stock that would enrage the current shareholders. For them this government funding might validate the scientific platform of the company, generate some revenue, and hype the stock.

Biotech industry executives state in private that if their capital markets strengthen they will be even less likely to consider Bioterror countermeasure research. One CEO whose company has received an NIH grant for Bioterror countermeasure research stated in private that his company would never have considered this entanglement with the government if it had any other options to fund its research.

Our goal with BioShield II should be to engage the successful biopharma companies in this research — companies that have brought products to the market — and persuade them that the government will be a reliable partner. Then the risk of failure and cost overruns is shifted to the industry and we've engaged the companies with a track record of bringing products to the market. The government will need to provide substantial rewards if – and only if – the companies do succeed in developing the medicines we need, but then the government is only paying for results. When the government funds the research, it funds a process with no guarantees of any success. Providing the industry with substantial rewards for success is a model that engages the industry as entrepreneurs, drawing on the greatest strength our nation has in the war on terror.

# Metrics for Success of Project BioShield

With the enactment of BioShield, it is critical for the Administration and Congress to agree on metrics for determining whether BioShield is sufficient. We also should immediately launch a comprehensive review of the policy options available to supplement it — with this hearing a perfect start for such review.

In terms of metrics to measure the success of Project BioShield, let me suggest that we are on the right track if we see the following response:

1. Government, academia and industry set a long-term research and development agenda — decades long — that is commensurate with the full range of current and evolving bioterror threats;
2. The research and development agenda focuses in part on development of powerful research tools that will enable us to respond quickly to a new, unforeseen terror agent and not just to develop countermeasures for terror agents we know about today;
3. Government determines that the key to success in developing bioterror countermeasures is securing the enthusiastic engagement of private biopharma companies pursuing the research for their own good business reasons as "profit marking arsenals";
4. Government understands and accepts the entrepreneurial culture of the biopharma industry and sees that it is not an industry that can be recruited for bioterror countermeasure research on the defense contractor model
5. Government is able to overcome the suspicions of the biopharma companies and establish itself as a reliable long-term partner in bring bioterror countermeasure research to a successful conclusion and the Government reassures industry that what happened to Bayer in the Cipro case will never happen again;
6. We begin to see that a biodefense industry has become established, with its own capital funding from investors and retained earnings, its own lead companies, its own stock analysts, and its own legitimacy in the markets;
7. Successful biopharma companies are investing hundreds of millions of their own capital in bioterror countermeasure research and competing with one another to bring countermeasures to the market, small biotech companies are able to secure funding from investors for bioterror countermeasure research, and biotech companies are able to go public with IPOs for bioterror countermeasure research;
8. CFOs of biopharma companies see a reasonable opportunity to secure operating margins (rates of return) on their investment in bioterror countermeasure research that are commensurate with those that they seek and secure for other research;
9. We see company commitments to long-term research projects that might not yield a countermeasure for the 10-12 years — the industry average;
10. Government understands that it can shift significant risk to the biopharma companies as long as it provides a reasonable rate of return if and when the companies successfully complete their research;
11. Government understands that is must remain focused on results — countermeasures that can be stockpiled and deployed — rather than process;

12. Government funded basic research is focused so that it does not compete with that of private companies and its inventions are transferred to company partners expeditiously on commercially reasonable terms;

13. Government makes the FDA animal model rule work effectively when bioterror countermeasures are brought to it for review and approval;

14. We see renewal in the U.S. vaccine industry, which has essentially been destroyed by government regulation;

15. We see companies launching major research projects to develop the next generation of antibiotics and antivirals, with major benefits for other infectious and contagious diseases, including HIV/AIDS, malaria, TB and antibiotic resistant pathogens; and

16. Government is not concerned that bioterror countermeasure research might yield collateral commercial market benefits to companies and considers this a positive development.

These are ambitious metrics for success, and I am open to hearing the Administration's own proposed metrics. What we cannot afford to do is simply to spend two years trying to implement BioShield without applying metrics of success to every stage in the process.

In terms of exploring the policy options for BioShield II, the bills that Senator Hatch and I have introduced are comprehensive and ambitious. There are other possible options that might be appropriate. We are happy to work with the Administration and appropriate committees of the Congress to review them. At a minimum, this review should focus on liability, intellectual property, tax, antitrust and research tool issues and should engage the Justice, Commerce, Treasury Departments, Homeland Security, Defense, and Health and Human Services Department.

## Implementation of Project BioShield

The industry will now watch how HHS implements BioShield and how NIH responds to the march-in petition. I anticipate that the implementation of BioShield will be a painful process as HHS experiences the depth of industry skepticism about this research and this market. In fact, it's not clear which is more threatening form an industry perspective – no market or an exclusively government market. I anticipate that HHS will find that it will only be able to engage biopharma companies that have little or no success in securing development of FDA-approved products and that are dependent on government funding for the research. If HHS is able only to engage these companies, and able only to engage companies as defense contractors, it's prospects for securing development of the full range of medical countermeasures we need will be bleak.

HHS will be setting its long-term agenda of development projects. It has yet to be seen how HHS will set the mix of diagnostics, therapeutics, and vaccines. Many believe that diagnostics and therapeutics are more important priorities than vaccines. Former Soviet bioweaponeer Ken Alibek and his colleague Charles Bailey argue that "vaccines are not a realistic prophylaxis for civilian populations, because they would be only

effective in very narrowly defined circumstances.[14] They argue that even if we had vaccines for the top six Bioterror pathogens, it is "highly unlikely that a decision would be made to vaccinate the entire population against each" of them. They argue that vaccines are "unlikely ever to be used…" They recommend we focus on medicines to treat the late stages of these diseases. Given the delay that may arise between an attack and the recognition of it as an attack, this would seem to be the most important priority for BioShield.

One key implementation issue has already arisen. My staff has heard that HHS is saying that it won't guarantee procurement of a medical countermeasure under BioShield unless the FDA has granted IND (investigational new drug) status to the medicine. It has referred companies to NIH for funding to take the product to that stage of development. This interpretation makes no sense and may substantially inhibit the effectiveness of BioShield. The concept behind BioShield is that the government will provide detailed specifications regarding the market for a medical countermeasures so companies can assess whether to risk their capital to develop the countermeasure. This concept applies to research and procurement of any medicine, including those that are long-term research projects that might take many years to reach the IND stage. Because BioShield is a procurement bill, not a research funding bill, and only guarantees procurement if and only if the country develops the product the government needs, there is little risk in applying BioShield to pre-IND research. Many companies have no interest in negotiating a research funding grant from NIH — they'd rather rely on investor funding or retained earnings — or might not receive a grant.

Perhaps this interpretation arises from the extremely limited funding for BioShield. The Tufts Center for the Study of Drug Development estimates that industry expends more than $800 million on average to develop a new chemical entity. It is clear that the $5.6 billion funding for BioShield procurement represents a fraction of what will be needed to develop all of the medical countermeasures we will need to prepare for a Bioterror, chemical or radiological attack. (By way of contrast, the government spent nearly $7 billion in just one year developing the missile defense system. Many believe we are much more likely to see a Bioterror than a missile attack.) As a way to ration its scarce funds, the IND requirement might be necessary, but as a development strategy it does not fully exploit the potential embodied in BioShield to shift the risk to the industry to fund the research in exchange for a specified reward for successful R&D projects.

The first Request for Proposal (RFP) for biodefense subsequent to the enactment of BioShield was issued on August 18[15] for immunotherapeutic antitoxins (e.g. monoclonal antibodies, polyclonal antibodies, and human immune globulin), other protein products (e.g. mutated toxins), and small molecule entity treatments (e.g. protease

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[14] Ken Alibek and Charles Bailey, "BioShield or BioGap," Biosecurity and Bioterrorism: Biodefense Strategy, Practice and Science, Volume 2, Number 2, 2004.

[15] http://www2.eps.gov/spg/HHS/OOS/OASPHEP/Reference%2DNumber%2D2004%2DN%2D01385/Attachments.html

inhibitors) for the treatment of inhalational anthrax. The RFP calls for the procurement of 10,000 -200,000 therapeutic courses of treatment, contingent upon the outcome of an initial procurement of "10 grams" of the product for the government to test – a surprisingly small amount. Many in industry found this RFP surprising, with its focus on an initial purchase of such small amounts of the product which will serve as a significant deciding factor in determining the fate of further acquisition of the product. This approach seems rather plodding, attenuated and cautious.

More troubling, there is no clear timeline for procurement of additional courses of treatment nor is there a predictable outcome for a contractor awarded only the initial phase of the contract. There seems to be no limitation on the company selling the same product in other markets, including allies or civilian markets.

The RFP indicates that even though the company, at the time of award, has obtained an IND from the FDA to proceed with human clinical trials, HHS will be reviewing the IND data on its own and conduct its own comparative testing, after which it might conclude that it will not go forward with a contract with the company. Given FDA's special expertise on these matters and their designated mission to protect public health by ensuring safety and efficacy of medical products, it is not clear what other government agency might find to trump the FDA determination. Does HHS have a specific animal model or in vitro test that they find particularly relevant, different from any communicated by the FDA during the IND process that the company hasn't performed? It is not clear why HHS requires only that the IND be filed, and not requiring that it be approved at the time of application. It is not clear in the RFP how soon HHS will make its final determination. Will it wait until the FDA has approved or denied an IND for all companies who submitted proposals, or for some subset? What if the FDA approval of the IND sets standards for the clinical trial in excess of those upon which the bid price is premised?

Other terms of the RFP are less surprising. The intellectual property associated with the product appears to remain the property of the company. The contract asks for offers from companies for the fixed total contract price (with some items being cost reimbursable that needlessly subjects the winner to implement very burdensome cost accounting processes, thus further discouraging industry participation), more than one contract might be issued, and the company must first submit a "complete IND" application to the FDA for the initiation of human clinical trails. INDs can only be obtained after the company has completed toxicity and other laboratory tests that demonstrate that the product is "reasonably safe to give to human subjects in clinical trails." The RFP requires that the company show "proof of concept in small animals." The contractor must commit to securing final FDA approval for the product. The contractor shall be required "to attempt to obtain clinical trial insurance" but can request HHS to invoke the Safety Act for the work, thereby leaving a bidder's position on liability to be tenuous at best. The company is required to establish a security plan for the development, manufacturing, storage and distribution of the product. The company is required to maintain a production line for the product through the life of the contract. The experience of the bidders is one relevant factor in determining which will be

selected. About 100 complex FAR provisions will be included in the contract, all with their own interpretations and enforcement issues. Strangely the contract takes advantage of none of the special contracting authority found in BioShield, which can be used to cut through some of burdensome and intimidating FAR contracting provisions.

In addition, many of the standard "special contract requirements" are not appropriate for biodefense contracts and should be tailored accordingly. For example, the requirement for incorporation of the technical proposal into a contract would make this information publicly available. Not only does this pose the risk of exposing proprietary data to competitors, but it also creates a national security risk, allowing potential development by terrorist organizations of strains that can evade the specific countermeasure which is being developed for stockpiling and make such countermeasure ineffective.

Responses to the RFP are due October 19, 2004 and we will then see whether this HHS approach is proving to be effective in securing the engagement of biopharma companies with a proven track record of bringing products to market. We must then wait for the first procurement under Project BioShield to go forward.

We anticipate that the implementation process will be a difficult one as HHS learns more about what terms and limitations are acceptable to the companies it wishes to bid and which are considered threatening or unduly burdensome. Given the operating margins for these companies, the fixed price for these contacts might be a huge issue. When the Joint Vaccine Acquisition Program (JVAP) at the Department of Defense put out a solicitation for the procurement of seven vaccines, not a single established pharmaceutical company chose to bid.

## BioShield II Provisions

The BioShield II legislation we will introduce will be based on S. 666, legislation Senator Hatch and I introduced on March 19, 2003, and from which BioShield was taken. While BioShield establishes a predictable and guaranteed government market for medical countermeasure for Bioterror pathogens, BioShield II will include tax incentives to form capital for biopharma companies to conduct research to develop these countermeasures, protect and enhance intellectual property associated with these countermeasures and address other issues that affect the companies' inclination to conduct this research.

The premise of this legislation, as it was with BioShield, is that direct government funding of this research is likely to be much more expensive and risky to the government and less likely to produce the countermeasures we need to defend America. Shifting some of the expense and risk of this research to entrepreneurial private sector firms is likely to be less expensive and much more likely to produce the countermeasures we need to protect ourselves in the event of an attack.

The legislation will provide that a company seeking to fund research is eligible to elect from among three tax incentives:

(a). Establishment of an R&D Limited Partnership to conduct the research. The partnership passes through all business deductions and credits to the partners.

(b). Issuance of a special class of stock for the entity to conduct the research. The investors would be entitled to a zero capital gains tax rate on any gains realized on the stock.

(c). Receive a special tax credit to help fund the research

The first two provisions help small biotech companies to form capital to fund the research. These companies cannot use tax credits because they have no revenue from product sales and no income tax liability with respect to which to claim a tax credit.

The legislation will provide that a company that successfully develops a countermeasure is eligible to elect one of two patent incentives:

(a). The company is eligible to receive a patent for its invention with a term as long as the term of the patent when it was issued by the Patent and Trademark Office, without any erosion due to delays in the FDA approval process.

(b). The company is eligible to extend the term of any patent owned by the company for two years. The patent may not be one that is acquired by the company from a third party. In S. 666, this wild card patent provision is only available to companies with $750 million or less in paid-in capital.

In addition, a company that successfully develops a countermeasure is eligible for a 10-year period of market exclusivity on the data supporting FDA approval of the countermeasure.

The legislation will provide for protections against liability for the company that successfully develops a countermeasure.[16] It will grant companies with a limited

[16] One issue to address regarding liability is protection for those administering, distributing, and overseeing the administration and distribution of the Strategic National Stockpile ("SNS") and other emergency uses authorized under the Project BioShield Act. Health care providers, including health care workers and volunteers who assist them, and local government agencies and their employees are on the front lines of defense after such an attack or other emergency develops, especially in densely populated metropolitan areas. The efficient administration of prophylaxis and other countermeasures designed to prevent the spread of disease or to provide antidotes to victims of an attack or other emergency is critical. Legitimate concern about liability can seriously hamper relief efforts by health care providers, local government agencies, and a wide range of individuals.

Such liability protection currently exists for measures to prevent and treat smallpox. Section 224(p) of the Public Health Service Act, 42 USC § 233(p), provides for Federal Tort Claims Act protection for "covered persons", which include health care entities, local government agencies, and other persons and entities involved in the administration of smallpox countermeasures, including vaccina inoculation. There appears to be no reason to limit liability protection to smallpox countermeasures given what we know about the threat posed by other forms of attack, such as anthrax. The SNS

exemption from the antitrust laws as they seek to expedite research on countermeasures. It will include special incentives are incorporated to ensure that manufacturing capacity is available for countermeasures. And it will apply all of the incentives to the development of research tools.

Given the reluctance of the biopharma industry to participate in the legislative process on BioShield, it's been difficult to determine whether enactment of these BioShield II incentives will be sufficient to establish a biodefense industry. I believe that doing less will not be sufficient, but I acknowledge that even if we enact every provision in BioShield II, we may not meet all of the metrics of success that I have proposed.

We should not stop until we have reached our goal – to establish a well capitalized and expert biodefense industry to develop these medical countermeasures. We must recognize that our challenge is not simply to procure and stockpile a few diagnostics, therapeutics and vaccines. The Bioterror threat is evolving rapidly and over time we will need to develop many additional medicines. We need a biodefense industry ready, willing, and able to accomplish this mission.

To do this, we need to reassure the biopharma industry that the government will be a reliable partner in this research and persuade the industry that what happened to Bayer in the Cipro procurement will not happen to them. Most of all, we need to engage the successful biopharma companies – the ones that have a track record of bringing safe and effective medicines to market. We need to engage these companies as entrepreneurs, not as defense contractors. Acting as entrepreneurs, deploying their own or investor's capital, we can shift some of the risk of this research to the industry. If we seek to engage

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includes vaccines, antitoxins, antivirals, chemical agent antidotes and other emergency medications and supplies for a vast array of public health emergencies. Similarly, emergency uses under the Project BioShield Act potentially include other drugs, biological products and devices developed to treat, identify or prevent biological, chemical and radiological attacks.

One approach would be to apply liability protection to SNS assets and emergency uses authorized under the Project BioShield Act similar to what is currently provided for smallpox. Persons covered under the proposed amendment would be the same. Moreover, as with the protection afforded to those carrying out research and development contracts under the Project BioShield Act (section 319F-1(d)(2)-(3) of the Public Health Service Act), this approach would permit recourse by the United States in cases of gross misconduct by covered persons and authorize the Secretary of Health and Human Services to institute procedures to determine who is entitled to protection.

Unfortunately, a response to a biological, chemical or radiological attack or any other public health emergency sometimes requires broad, prophylactic measures to prevent extensive casualties or a catastrophic spread of disease not known in this country for more than 80 years. In order to be fully prepared, we must consider how to ensure that those administering, distributing, and overseeing the administration and distribution of measures to stop or mitigate the effects of such an attack or emergency are not exposed to unnecessary liability.

these companies as defense contactors, it's likely to cost more with fewer prospects for securing the development of the medicines we need.

The single most controversial proposal in BioShield II will be the wild card patent extension. There will be substantial debate on this proposal and both sides have legitimate concerns. In favor of it is the concern that without it we will not be able to establish a biodefense industry. Against it is the concern that it will unfairly raise health care costs to consumers and health care entities. The Congress has looked at similar points before and decided to extend patents on drugs as an incentive for companies to conduct pediatric clinical trials and secure appropriate pediatric labels. In this case Congress judged that the patent extensions were worth their cost. The details of how the wild card patent provision would work are also important and we are open to discussing them. In the end, Congress will have to weigh the competing considerations and judge whether we should include the wild card patent as an incentive.

If BioShield II is insufficient to accomplish these goals, we need to develop BioShield III. We must do whatever it takes to ensure that we have the medical countermeasures available if and when there is a Bioterror attack. The consequences of failing to do this could be catastrophic. We cannot settle for some effort to develop these countermeasures – we need results, not process.

## Who Should Be In Charge?

BioShield is being implemented by the Department of Health and Human Services. The bills that Senator Hatch and I have introduced place the implementation responsibility with the Department of Homeland Security. The Department of Defense is a third alternative, but its efforts to develop Bioterror medical countermeasures have been a scandalous failure. We need a frank and full review of which agency has the best culture and expertise to lead this vital effort.

HHS has a complicated and often contentious relationship with the biopharma industry. The industry has had frequent policy conflicts with the Food and Drug Administration, The Center for Medicare Services and the National Institutes of Health. Over many decades we've seen HHS focused on keeping unsafe and ineffective products off the market, reducing the government reimbursement for medicines, and policies that are hostile to patents. The original version of BioShield submitted to the Congress by the Administration was laced with provisions that the industry viewed as dysfunctional, unworkable, and hostile. Given this history and culture, it is not clear that HHS can effectively work with the industry on a massive industrial development program with regard to Bioterror countermeasures. HHS does substantial scientific and contracting expertise.

The Department of Homeland Security appears to be developing a culture that focuses intensively on the bottom line with no time taken for ideological diversions. It has no history of conflicts with the biopharma industry. It does not now possess substantial scientific and contracting expertise.

The issue of who is in charge is central to all of our homeland security issues. That's why I first proposed that we create a Department of Homeland Security. We should review carefully the effectiveness of HHS in implementing BioShield, its metrics for determining whether BioShield is sufficient, and its review of the policy options for supplementing BioShield. If HHS does not perform well in these roles, we should consider whether the Department of Homeland Security might provide better leadership.

# Research Tools

We will never be able to anticipate all of the pathogens that might be utilized by terrorists. Our medicine chest will never have all the medicines we need for all the possible terrorist pathogens. The ultimate and only effective bioterror defense are "research tools" powerful enough so that we can develop and deploy a new countermeasures quickly after an attack has occurred. We need this power to respond to Mother Nature's new concoctions, like SARS, but it's also the only defense against exotic terror pathogens we'll never see in advance of an attack. As stated by the leading biodefense think tank,

> The process of moving from 'bug to drug' now takes up to ten years. The U.S. biodefense strategy must act as one of its key strategic goals the radical shortening of this process.[17]

The development of research tools is a central focus of the bills that Senator Hatch and I have introduced and it will be a central focus in BioShield II and all of the incentives in BioShield II will apply to the development of research tools.

One obstacle to the development of research tools to expedite the development of Bioterror countermeasures is the NIH Research Tool Guidelines. Finalized in 1999, the guidelines[18] find that "intellectual property restrictions can stifle the broad dissemination of new discoveries and limit future avenues of research and product development." It defines a "research tool" in "its broadest sense to embrace the full range of tools that scientists use in the laboratory, including cell lines, monoclonal antibodies, reagents, animal models, growth factors, combinatorial chemistry and DNA libraries, clones and cloning tools (such as PCR), methods, laboratory equipment and machines." A more sweeping definition is hard to imagine. With regard to these tools, the guidelines find that patents, and "reach-through royalty or product rights, unreasonable restraints on publication and academic freedom, and improper valuation of tools impede the scientific

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[17] Bradley T. Smith, Thomas V. Inglesby, and Tara O'Toole, "Biodefense R&D: Anticipating Future Threats, Establishing a Strategic Environment," BioSecurity and Bioterrorism: Biodefense Stategy, Practice, and Science, Volume 1, Number 3, 2003.

[18] PRINCIPLES AND GUIDELINES FOR RECIPIENTS OF NIH RESEARCH GRANTS AND CONTRACTS ON OBTAINING AND DISSEMINATING BIOMEDICAL RESEARCH RESOURCES, Federal Register Notice published on Thursday, December 23, 1999, 64 FR 72090.

process whether imposed by a not-for-profit or for-profit provider of research tools." While the NIH guidelines only apply to recipients of government funding, the guidelines states that "it is hoped that other not-for-profit and for-profit organizations will adopt similar policies and refrain from seeking unreasonable restrictions or conditions when sharing materials."

The practical result of the guidelines is that any private company that seeks to develop research tools must be wary of working with any institution or individual that receives NIH grants. This estranges the industry from the academic community with regard to the development of these tools. In many cases, the innovative research of academics had led to the private sector development of tools by companies whose business plan was to create such tools, not develop therapeutics. Now it is much less likely that the work of academics regarding research tools will ever be commercialized. This could not be worse timing – what we need to prepare for a Bioterror attack is a well capitalized research tool industry. Accordingly, our bills waive the application of the research tool guidelines to tools relevant to the development of Bioterror countermeasures. These tools are the gold standard for preparedness for a Bioterror attack.

Finally, the Food and Drug Administration has published a rule that permits Bioterror medical countermeasures to be developed relying on tests in animals rather than humans. This is necessary as it is not ethical to test a Bioterror pathogen on a human subject and there is no patient population available with a naturally occurring incidence of these diseases. One major issue for the development of these countermeasures is whether animal models exist for the diseases for which we need to develop countermeasures. If there is no animal model for a disease, it is not likely that biopharma companies will begin a research project to develop a countermeasure when there is no path to FDA approval. In addition, there is a growing shortage of animals.[19] We need to take decisive action to ensure that this research tool does not prove to be a major bottle neck in the R&D to develop Bioterror countermeasures.

# Third World Diseases and Antibiotic Resistant Pathogens

As we draft BioShield II, we are actively exploring the scientific and economic implications of applying BioShield and BioShield II to infectious diseases generally, not just pathogens deemed to be "terror weapons."

As a matter of science, the research and development on countermeasures to bioweapons is inextricably linked to research directed to pathogenic virus, bacteria and fungus that cannot be weaponized. Consequently, it makes sense to enact incentives for

[19] See Michael Hopmeier, President/CEO of Unconventional Concepts, "Too Many Germs, Too Few Monkeys: The Shortage of Non-Human Primates, Clinical Research, and Test Infrastructure," FDLI Update (March/April 2004).

research that addresses the pathology, diagnosis or therapeutics that relates to virus bacteria or fungus whether it has been or could be weaponized or not. Research on infectious diseases seeks to understand how organisms cause disease, the immune system responds to pathogens, and antibodies and other medicines protect against them. This research is broadly applicable to both bioterror and non-bioterror pathogens. In the end, we need broad-spectrum antibiotics, anti-virals that can be utilized against a variety of viruses, and vaccines that can be adapted to a variety of organisms.

As enacted into law, BioShield could be applied to the development of new antibiotics, which can serve as a Bioterror countermeasure. The Administration's draft of BioShield provided that if there was a "significant commercial market for the product other than as a homeland security threat countermeasure" BioShield would not apply (S. 15, section 203, as introduced on March 11, 2003). This anti-dual use provision, which would have squandered the potential benefits of this legislation for the development of new antibiotics and other dual-use medicines, was deleted in the final version of the bill. We need these antibiotics as countermeasures for Bioterror pathogens and we especially need them to respond to Bioterror pathogens that are engineered to be antibiotic resistant.

We also need new antibiotics to respond to a public health crisis in our hospitals – one documented in great depth by the Infectious Diseases Society of America in Bad Bugs, No Drugs (July, 2004). IDSA finds that about 70% of the two million bacterial infections in America each year are resistant to at least one antibiotic. If our current range of antibiotics loses its effectiveness – and signs of resistance to our last line of antibiotics, vancomycin, are appearing – then we will face a public health crisis even if there is never a Bioterror attack. The relentless rise of antibiotic resistance in bacteria and the exit of all of the major Pharma companies conducting R&D in this area due to lack of incentives will leave us vulnerable in the extreme by the end of the decade. At some point society will be badly bitten by this trend, with pandemic influenza being the most likely candidate in the short term. I fear that someday we'll be forming another 9/11 commission after large numbers of Americans (and others around the world) die as a result of failure of our government to engage the problem proactively.

While BioShield could apply to the development of new antibiotics, it is not likely that new antibiotics will be listed as a priority of the Administration for Project BioShield. BioShield focuses on procurement by the government of medical countermeasures, so it is likely that it will mostly or entirely be utilized for procurement of countermeasures where the government is the sole market. There is a substantial civilian market for antibiotics, with the government only a marginal player. It makes more sense to deploy the tax, intellectual property, and other incentives in BioShield II to this research. This would both be consistent with our needs for Bioterror preparedness and provide a much-needed benefit to our public health infrastructure.

In terms of infectious disease generally, it is likely that the biopharma companies that we might engage in developing Bioterror countermeasures will have expertise and capital from investors for research on a broad range of infectious diseases, going well beyond those that might be weaponized. In fact, it may well be easier for these

companies to form or deploy capital for this research if it involves development of medicines where the Federal government is not the sole or principal market. In the end, we need to establish an Infectious Disease Industry, not just a BioDefense Industry. We need companies capable of development effective platforms that have a broad application to a variety of infectious diseases — research tools of immense power and importance. We certainly need many more companies with expertise in developing vaccines. So, it makes little economic sense to stovepipe these lines of research, providing incentives for research to develop medicines for only a select few pathogens we label as "bioterror pathogens." It is also true that in some cases we may not know if a particular pathogen can be weaponized. For example, some believe SARS could be weaponized.

Accordingly, it makes good sense to apply BioShield II to research and development of countermeasures for "infectious" diseases even if they might not be pathogens that can be weaponized. BioShield could also be applied to these countermeasures with a proviso that the government could organize a procurement fund comprised of its own funds, funds form international public health agencies like the Global Alliance for Vaccines and Immunization (GAVI), foundation funding, and other sources. This is an issue that we need to explore with organizations such as the IDSA, The international Aids Vaccine Initiative, the Alliance for Microbicide Development, the Alan Guttmacher Institute, the AIDS Vaccine Advocacy Coalition, Biotech Ventures for Global Health, the Aeras TB Foundation, AmFAR, the Global Alliance for TB Drug Development, the Malaria Vaccine Initiative (MVI), International Partnership for Microbicides, Medicines for Malaria, and similar groups.

The need for additional research to develop therapies, cures, and vaccines for infectious disease – both Bioterror and natural – is clear. Worldwide, seventeen million deaths annually are caused by infectious and parasitic diseases, 33% of the total and 71% of all deaths among children under 5 years of age. This compares with fourteen million deaths from famines, wars, violence and aging, the same number from circulatory and obstructive pulmonary disease, and five million due to cancer. AIDS is out of control in many countries and mutating to create new strains. In the end, we may lose one hundred million people to AIDS. Malaria is developing resistance to the newest prophylaxis – with nearly three million deaths a year. Antibiotic resistant TB is surging – with over three million deaths a year. One million die each year of hepatitis B and one billion are infected. 165,000 each year die of hookworm and roundworm. We have seen waves of emerging diseases, including AIDS, SARS, West Nile virus, Lyme disease, and hantavirus. The public health agenda – for bioterrorism and beyond – is compelling and amply justifies enactment of new incentives for development of effective medical countermeasures.[20]

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[20] Incentives for research on Third World diseases have been proposed before. On May 16, 2001 Senators Kerry and Frist introduced S. 985, The Vaccines for the New Millennium Act of 2001. An identical bill was introduced in the House by Representative Pelosi on April 4 (See H.R. 1504).

S. 895 and H.R. 1504 proposed the enactment of two tax credits for research and sales of vaccines and microbicides for malaria, TB, HIV or "any infectious disease (of a

single etiology) which, according to the World Health Organization, causes over 1,000,000 human deaths annually." It did not apply to diseases with fewer deaths but much greater incidence. The new credit for research was set at 30%, which compares to the current 20% R and D Tax Credit. The bill bared any credit for any vaccine research (other than human clinical testing) conducted outside the United States. The credit was made "refundable" for corporations with "aggregate gross assets" of less than $500,000,000, zero tax liability in the preceding two years, and the corporation pledges to apply the refund to the vaccine or microbicide research. This made it useful to small biotech companies with no approved products, no sales revenue and no tax liability with respect to which to apply a tax credit. No carrybacks of the credit were permitted for research that had previously been performed. The sales tax credit was for the amount it is reimbursed sales of these vaccines and microbidies to a nonprofit organization or foreign government for distribution in a developing country. This credit makes the sales income tax exempt, increasing its value by about 35% (the marginal tax rate of most corporations). This credit was not refundable, and a $100 million limit was set on the available credit for the first five fiscal years and a $125 million limit for the next four years. This budget for the credit was to be allocated by the U.S. Agency for International Development. In addition, the legislation established a "Lifesaving Vaccine Purchase Fund," with the purchases to be made "at prices which take into account the seller's research, development, and manufacturing costs and the desirability of the vaccine purchased."

The legislation includes the following statement regarding distribution of the vaccines developed using the research credit: "Given the important goal of ensuring that all those in need, in both industrialized and developing countries, reap the benefits of any vaccine or microbicide that is developed for HIV, tuberculosis, or malaria, and acknowledging the importance of intellectual property rights and the right of corporations and shareholders of corporations to set prices, retain patent ownership, and maintain confidentiality of privileged information, corporations and shareholders of corporations who elect to take the credit under section 45E of the Internal Revenue Code of 1986, as so added, for research expenses incurred in the development of a vaccine or microbicide shall certify to the Secretary of the Treasury that, not later than the date which is 1 year after the date on which the vaccine or microbicide is first licensed, such corporation will establish a plan to maximize distribution of such vaccine or microbicide in the developing world using such mechanisms as technology transfer, differential pricing, and in-country production where possible, or other mechanisms to maximize international access to high quality and affordable vaccines." It also acknowledged that "Flexible or differential pricing for vaccines, providing lowered prices for the poorest countries, is one of several valid strategies to accelerate the introduction of vaccines in developing countries."

In 2001, Senator Kerry secured inclusion of a tax credit for research on vaccines and microbicides for tropical diseases in the Senate version of H.R. 1836, the Republican tax cut legislation. (See Section 811). The credit was for research, it was set at 30% (compared to the current R&D Tax Credit of 20%), it did not cover sales of any such vaccine or microbicide, and it was not refundable (so it could not be used by any company with no tax liability, which is 95% of the biotech industry). It was scored by the

# National Institutes of Health Reform

BioShield and BioShield II are directed at the biopharma companies. These companies have the expertise and experience needed to develop medical countermeasures; government does not. There remains an important role for government funded basic Bioterror research, principally through the National Institutes of Health. We need to be sure that these basic research investments implement a sophisticated strategy, with a clear understanding of how this research supports, and does not conflict with or duplicate, research that is more appropriately conducted by the biopharma companies.

The patent restoration provisions of BioShield II are especially critical to patents on basic research. Inefficiencies in the technology transfer process and the long-lead time necessary to translate basic research into FDA-approved products means that patents on basic research tend to be eroded. The patent term runs from the date of application, not the date of FDA approval, so if there are delays between the grant of a patent and FDA approval, much of it can be lost. If a patent has eroded 3-4 years, and additional erosion can be anticipated, it is likely that the patent will never be commercialized, it will block other researchers while it is in effect, and then it will die. Unpatentable inventions tend not to be commercialized by the biopharma industry.

As Anthony Fauci, the Director of NIAID, has acknowledged that "the path to product development has not been a part of [NIAID's] research strategy."[21] NIH translates its basic research into commercial products through technology transfer licenses with biopharma companies. For a variety of reasons, including the imposition of the reasonable price clause, the threat of march-in rights, the NIH research tool guidelines and other policies, NIH's technology transfer program has not be notably successful.

A variety of measures should be considered to strengthen this critical program.

1. The commercialization efforts at NIH could be consolidated, centralized and restructured within a new National Center for Health Care Technology Development. It could be headed by a Director subject to Senate confirmation.
2. The Center's mission could be to increase the yield of our current investment in biomedical research and make the commercialization efforts more responsive to the medical needs in this country and more transparent to the taxpayers and their elected representatives.
3. The Center could oversee NIH's technology transfer programs, patenting and licensing of patents, and set a research and development strategy for NIH sponsored research.
4. The Center could gather and publish detailed measures of NIH's success in ensuring that its basic research is developed into commercial products.

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Joint Tax Committee as losing $1.547 billion over ten years (See JCX-48-01)(May 24, 2001) It was deleted in the conference and did not become law.

[21] Fauci AS. Biodefense on the Research Agenda. Nature, 2003: 421: 787.

5. The Center could be the liaison with the NIH grantees on all issues involving technology transfer.

6. Restrictions could be lifted that reduce the ability of NIH to act in a more entrepreneurial manner. This will allow NIH to foster the growth, by investing in and sponsoring technology that is emerging and entering into the commercial research market.

7. NIH and each Institute could consult with an industry advisory board to insure its research agenda is supportive of and not duplicative of industry research.

8. The process for selecting grantees could include assessments of the opportunities that may exist for commercialization of the sponsored research.

9. Grantees success in bringing technology to patients could be tracked so that the successful programs might be recognized, rewarded and copied by others

10. The Center could be charged with teaching what it learns to the research community in this country and around the world.

In addition, I have proposed I have proposed creating an American Center for Cures, which would be connected with the National Institutes of Health. Its job would not be to engage in much original research, but rather to better organize and fund work already being done in government and private laboratories across the country.

Right now, there is not only duplication of effort, but efforts are uncoordinated. Different laboratories may have keys to different pieces of the puzzle and be completely unaware of each other's work.

The Center for Cures would connect these efforts.

The Center for Cures would also work with the scientific community and the private sector to support the promising lines of research, even on those drugs and antibiotics that, while unprofitable, are indispensable if it is you or a family member who need them.

When leads looked promising, the Center would be able to commission large-scale research across disciplines to take advantage of advances not only in biology, but also in the physical sciences, computer science, and engineering.

The Center for Cures would also work with the pharmaceutical and biotechnology industries – especially smaller firms – to create incentives for innovation as well as cutting through bureaucracy to make it quicker and easier to get cures from the researcher's bench to the patient's bedside.

# Responding to a Declaration of War

We should not need a 9/11 Commission report to galvanize the Administration and the Congress to respond to the unprovoked and deadly Bioterror attacks of three years ago. The threat could not be more obvious and what we need to do is also obvious. If we don't develop the diagnostics, therapeutics, and vaccines to protect those who

might be exposed or infected, we risk public panic and quarantines. We have the world's preeminent biopharma industry and we need to put it to work in the national defense.

BioShield is a step in the right direction, but it is a small step that does not take us where we need to go. We need to follow the implementation of BioShield very carefully and set clear metrics for determining its effectiveness. We should not wait to begin to review the policy options available to supplement BioShield. Senator Hatch and I will be proposing BioShield II and we will press for its consideration. We should press the biopharma industry to present its views on what it will take to engage it in this research and what it will take to establish a biodefense, research took, and infectious disease industry.

The American philosopher, George Santana said, "Those who cannot remember the past are condemned to repeat it." It's only been three years since the anthrax attack but I fear our memory of it already has faded. Let this hearing stand as a clear statement that some of us in the Congress remember what happened and are determined not to permit it to happen again. War has been declared on us and we need to act as if we noticed.

# Appendix

Defense Science Board "stoplight chart" – The Projected Evolution of Diagnostics, Vaccines, and Therapeutics Against Major Bioagents with Strategic R&D and Supply Actions (Summer 2000)

"Move on BioShield to Aid Biodefense Industry," Senator Joe Lieberman and Senator Orrin Hatch, The Hill (May 19, 2004)

Chronology: Incentives for Research to Develop Countermeasures to Bioterror Pathogens

Outline: Biological, Chemical, and Radiological Weapons Countermeasures Research Act of 2003, S. 666 (Senators Lieberman and Hatch)

BioPharma vs. Defense Contractor Operating Margins

Interview—Serguei Popov, Journal of Homeland Security (November 13, 2000)

# Move on BioShield to Aid Biodefense Industry

Senator Joseph Lieberman and Senator Orrin Hatch
May 19, 2004 — The Hill

Anthrax hit the Senate in October, 2001 and Senators and staff took CIPRO to prevent infection. There was no panic and no one fell ill. This may have lulled us into a false sense of complacency.

In fact, we are woefully unprepared with diagnostics and medicines to respond to a bioterror attack. Four years ago the Defense Science Board found that we had only one of the 57 bioterror medical countermeasures we most need. Today we have two. If we don't have diagnostics, drugs, and vaccines, next time we could see panic. Our country simply does not have the medicines we need to respond to a bioterror assault, neither in the short term nor the long run.

So what must we do? For openers, one way we should enlist our innovative biotech industry into the business of developing diagnostics, vaccines, antibiotics, and other medical countermeasures that would control the massive disease and death we might see from a biological weapons attack. Funding basic research is no longer enough. We also need diagnostics and medicines ready to use.

Right now, our biotech industry is not conducting the necessary R&D to develop these countermeasures, primarily because there is no private sector commercial market for these products. Because we hope and pray that we'll never face an attack, government emergency stockpiles are the only market. So, we must create the equivalent of a private sector commercial market for which the bio-pharmacological industry *will want* to invest their own and investors' capital to develop bioterror countermeasures. The industry must be provided tax incentives so small biotech firms can form the capital to fund this research. It must be assured of intellectual property protections for those worried the federal government might in a crisis confiscate a countermeasure. And, it must have liability protections because many of these countermeasures cannot be fully tested in clinical trails.

Last year, we reintroduced the Biological, Chemical, and Radiological Weapons Countermeasures Research Act, an ambitious bill we first introduced in 2002 that would create the right conditions and incentives for private sector R&D on bioterror countermeasures. Once those incentives are in place, the industry and its investors would be paid if, and only if, they successfully develop the countermeasures we need. This approach shifts the risks off the taxpayer and onto the industry for the inevitable research failures. The government pays only for success, not process.

Furthermore, this breakthrough research won't be wasted if there is no bioterror attack. We desperately need to develop new antibiotics to replace those for which resistance is emerging. Even if no bioterror attack ever occurs, the work of the biotech industry could make significant progress toward finding cures for infectious diseases that are ravaging millions of people

Our bill complements the Administration's Project Bioshield. Project BioShield follows our lead by setting the terms in advance for government markets – our concept. It would give bio-pharmacological companies reliable commitments regarding the market they will tap if they risk their own capital to develop countermeasures. In all likelihood, Project Bioshield would result in the development of some new Bioterror antidotes. We

believe Congress should pass Project BioShield immediately. It's a step in the right direction.

We believe that more can and should be done to provide additional incentives to help infuse the biodefense industry with the talent and capital necessary to give us all the bioterror medicines we need. Bioterror is an evolving threat that could, over time, require development of dozens, perhaps hundreds, of medical countermeasures. The Lieberman-Hatch bill would pave the way for industry involvement sufficient to meet the potential need.

We will know that we've established a biodefense industry when hundreds of millions of dollars in company and investor capital are available to fund countermeasure research, and investors see a reasonable opportunity to profit to the same degree they do on investments in other biomedical research.

We urge Congress to move expeditiously on the President's BioShield bill and then take up BioShield II, a bill we'll introduce once BioShield is enacted. It will be based on our own bipartisan legislation. That combination will advance the process of building a biodefense industry to protect us from future biological attacks.

In the long run, we may face no greater threat than a bioterror pathogen. Now is the time to come together to ensure that we are ready with the medical countermeasures – and the public health infrastructure – to prevent panic and minimize what could otherwise be massive loss of life. We will continue to work with President Bush, our colleagues in the Congress, and other interested parties on this important matter.

# Chronology: Incentives for Research to Develop Countermeasures to Bioterror Pathogens

**Summer 2000 — Defense Science Board finds that we have only 1 of the 57 bioterror countermeasures we most need**

**October 5, 2001 — Bob Stevens, a photo editor at American Media in Boca Reton, Florida, dies of inhalation anthrax.**

**October 7, 2001—U.S. Centers for Disease Control and Prevention (CDC) reported that investigators had detected evidence that the deadly anthrax bacterium was present in the building where Stevens had worked.**

**October 12, 2001 — NBC employee in New York exposed to anthrax.**

**October 15, 2001 — Anthrax laced letter opened in Senator Daschle's Office in the Hart Senate Office Building. ABC News finds anthrax in its offices in New York.**

**October 18, 2001 — CBS news finds anthrax in its offices in New York.**

**October 19, 2001 — New York Post finds anthrax at its offices in New York.**

**October 21-22, 2001 — Washington, D.C. area postal workers are diagnosed with inhalation anthrax after two others had died.**

**October 31, 2001 — New York supply clerk Kathy Nguyen dies of inhalation anthrax.**

**November 21, 2001 — Connecticut woman, Dottie Lungren, dies of inhalation anthrax.**

**December 4, 2001 — Senator Lieberman introduces S. 1764, a comprehensive set of incentives for research on countermeasures for bioterror agents**

**October 15, 2002 — First Anniversary of Daschle Office anthrax attack – no Administration proposal submitted to the Congress**

**October 17, 2002 — Senators Lieberman and Hatch introduce S. 3148, a refined version of S. 1764**

**January 29, 2003 — President Bush in his State of the Union Address calls for Congress to enact Project BioShield; it is modeled on one of twelve key provisions in S. 3148 (guaranteed procurement incentives)**

**March 19, 2003 — Senators Lieberman and Hatch introduce S. 666, a further refined version of S. 3148**

**March 25, 2003 — Senator Gregg introduces S. 15 -- the text of BioShield as submitted by the President**

**May 15, 2003 — H.R. 2122 introduced -- the House version of BioShield**

**June 10-July 18, 2003 — Three House Committees report H.R. 2122**

**July 16, 2003 — House passes H.R. 2122**

**September 2, 2003 — Senator Gregg introduces S. 1504 -- legislation similar to S. 15**

**October 15, 2003 — Second Anniversary of the Daschle Office anthrax attack**

**November 24, 2003 — President signs Department of Defense Authorization Act, H.R. 1588, Public Law 108-136, which contains a version of BioShield**

**May 19, 2004 — Senate passes S. 15 on a vote of 99-0 with an amendment (a complete substitute) based on the House-passed bill. Amendment No. 3178. S. 15 is now pending in the House.**

**July 14, 2004 — House passes S. 15 414-2. It goes to the President for his signature.**

**July 21, 2004 — President signs BioShield into law as Public Law 108-276**

**Senators Lieberman and Hatch have announced that they will introduce BioShield II, which will re-propose eleven incentives from S. 1764, S. 3148, and S. 666 that were not included in BioShield.**

## BIOLOGICAL, CHEMICAL AND RADIOLOGICAL WEAPONS COUNTERMEASURES RESEARCH ACT OF 2003, S. 666

**Senators Lieberman and Hatch**

The legislation[22] proposes incentives that will enable biotechnology and pharmaceutical companies to take the initiative -- for good business reasons -- to conduct research to develop countermeasures, including diagnostics, therapeutics, and vaccines, to treat those who might be exposed to or infected by biological, chemical or radiological agents and materials in a terror attack.

The premise of this legislation is that direct government funding of this research is likely to be much more expensive and risky to the government and less likely to produce the countermeasures we need to defend America. Shifting some of the expense and risk of this research to entrepreneurial private sector firms is likely to be less expensive and much more likely to produce the countermeasures we need to protect ourselves in the event of an attack.

For biotechnology companies, incentives for capital formation are needed because most such companies have no approved products or revenue from product sales to fund research. They rely on investors and equity capital markets to fund the research. These companies must focus on research that will lead to product sales and revenue and end their dependence on investor capital. When they are able to form the capital to fund research, biotech companies tend to be innovative and nimble and focused on the intractable diseases for which no effective medical treatments are available. Special research credits for pharmaceutical companies are also needed.

For both biotech and pharmaceutical companies, there is no established or predictable market for these countermeasures. Investors and companies are justifiably reluctant to fund this research, which will present technical challenges similar in complexity to development of effective treatments for AIDS. Investors and companies need assurances that research on countermeasures has the potential to provide a rate of return commensurate with the risk, complexity and cost of the research, a rate of return comparable to that which may arise from a treatment for cancer, MS, Cystic Fibrosis and other major diseases or from other investments.

President Bush's BioShield initiative is designed to establish and predictable market for these countermeasures. This legislation provides a template for implementation of BioShield and supplements it with additional incentives to ensure that the industry is enthusiastically engaged in this vital research.

The legislation provides tax incentives to enable companies to form capital to conduct the research and tax credits usable by larger companies with tax liability with

[22] The legislation was originally introduced by Senator Lieberman on December 4, 2001 as S. 1764. It was reintroduced by Senators Lieberman and Hatch on October 17, 2002, as S. 3148.

respect to which to claim the credits. It provides a guaranteed and pre-determined market for the countermeasures and special intellectual property protections to serve as a substitute for a market. Finally, it establishes liability protections for the countermeasures that are developed.

Section 3 of the legislation is drafted as an amendment to the Homeland Security Act of 2002 (HSA) (P.L. 107-296). Section 2 sets forth findings and sections 4-9 are drafted as amendments to other statutes.

1. Setting Research Priorities (Section 1811 of HSA): The Department of Homeland Security sets the countermeasure research priorities in advance. It focuses the priorities on threats for which countermeasures are needed, and with regard to which the incentives make it "more likely" that the private sector will conduct the research to develop countermeasures. It is required to consider the status of existing research, the availability of non-countermeasure markets for the research, and the most effective strategy for ensuring that the research goes forward. The Department then provides information to potential manufacturers of these countermeasures in sufficient detail to permit them to conduct the research and determine when they have developed the needed countermeasure. The Department is responsible for determining when a manufacturer has, in fact, successfully developed the needed countermeasure.

2. Registration of Companies (Section 1812 of HSA): Biotechnology and pharmaceutical companies register with the Department to become eligible for the incentives in the legislation. They are obligated to provide reports to the Department as requested and be open to inspections. The Department certifies which companies are eligible for the incentives.

Once a company is certified as eligible for the incentives, it becomes eligible for the tax incentives for capital formation, and if it successfully develops a countermeasure that meets the specifications of the Department, it becomes eligible for the procurement, patent, and liability provisions.

3. Diagnostics (Sections 1813 and 1814 of HSA): The incentives apply to development of detection systems and diagnostics, as well as drugs, vaccines and other needed countermeasures.

4. Research Tools (Section 1815 of HSA): A company is also eligible for certification for the tax and patent provisions if it seeks to develop a research tool that will make it possible to quickly develop a countermeasure to a previously unknown agent or toxin, or an agent or toxin not targeted by the Department for research.

5. Capital Formation for Countermeasures Research (Section 1821 of HSA; also section 4 of the legislation): The legislation provides that a company seeking to fund research is eligible to elect from among four tax incentives. The companies are eligible to:

(a). Establish an R&D Limited Partnership to conduct the research. The partnership passes through all business deductions and credits to the partners.
(b). Issue a special class of stock for the entity to conduct the research. The investors would be entitled to a zero capital gains tax rate on any gains realized on the stock.
(c). Receive a special tax credit to help fund the research.
(d). Receive a special tax credit for research conducted at a non-profit and academic research institution.

A company must elect only one of these incentives and, if it elects one of these incentives, it is then not eligible to receive benefits under the Orphan Drug Act. The legislation includes amendments (Section 9 of this legislation) to the Orphan Drug Act championed by Senators Hatch, Kennedy and Jeffords (S. 1341). The amendments make the Credit available from the date of the application for Orphan Drug status, not the date the application is approved as provided under current law.

6. Countermeasure Purchase Fund (Section 1822 of HSA): The legislation provides that a company that successfully develops a countermeasure -- through FDA approval -- is eligible to sell the product to the Federal government at a pre-established price and in a pre-determined amount. The company is given notice of the terms of the sale before it commences the research.

7. Intellectual Property Incentives (Section 1823 of HSA; also section 5 of this legislation): The legislation provides that a company that successfully develops a countermeasure is eligible to elect one of two patent incentives. The two alternatives are as follows:

(a). The company is eligible to receive a patent for its invention with a term as long as the term of the patent when it was issued by the Patent and Trademark Office, without any erosion due to delays in the FDA approval process. This alternative is available to any company that successfully develops a countermeasure irrespective of its paid-in capital.
(b). The company is eligible to extend the term of any patent owned by the company for two years. The patent may not be one that is acquired by the company from a third party. This is included as a capital formation incentive for small biotechnology companies with less than $750 million in paid-in capital, or, at the discretion of the Department of Homeland Security, to any firm that successfully develops a countermeasure.

In addition, a company that successfully develops a countermeasure is eligible for a 10-year period of market exclusivity on the countermeasure.

8. Liability Protections (Section 1824 of HAS; also Section 10 of the legislation): The legislation provides for protections against liability for the company that successfully develops a countermeasure.

9. Accelerated Approval of Countermeasure (Section 1831 of HSA): The countermeasures are considered for approval by the FDA on a "fast track" basis.

10. Special Approval Standards (Section 6 of this legislation: The countermeasures may be approved in the absence of human clinical trails if such trails are impractical or unethical.

11. Limited Antitrust Exemption (Section 7 of this legislation): Companies are granted a limited exemption from the antitrust laws as they seek to expedite research on countermeasures.

12. Biologics Manufacturing Capacity and Efficiency (Section 1832 and 1833 of HSA; and section 8 of this legislation): Special incentives are incorporated to ensure that manufacturing capacity is available for countermeasures.

13. Strengthening of Biomedical Research Infrastructure (Section 1834 and 1835 of HSA): Authorizes appropriations for grants to construct specialized biosafety containment facilities where biological agents can be handled safely without exposing researchers and the public to danger (Section 216). Also reauthorizes a successful NIH-industry partnership challenge grants to promote joint ventures between NIH and its grantees and for-profit biotechnology, pharmaceutical and medical device industries with regard to the development of countermeasures and research tools (Section 217).

14. Annual Report (Section 1841 of HSA): The Department is required to prepare for the Congress an annual report on the implementation of these incentives.

15. International Conference (Section 1842 of HSA): The Department is required to organize an annual international conference on countermeasure research.

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# BioPharma vs. Defense Contractor Operating Margins

The operating margin for successful biopharma companies is 2.76 to 3.74 times as great as the operating margins for major defense contractors. This means that the defense contractor model will not work to engage biopharma companies in developing medical countermeasures for bioterror agents. Whether the successful bipharma companies are "too profitable" is a separate issue. The issue addressed here is the operating margin that successful biopharma companies seek and expect as they assess lines of research to undertake. If the operating margin for biodefense research is drastically less than the operating margin for non-biodefense research, it is not likely that these companies will choose to undertake biodefense research.

**The operating margin for the major defense contractors listed below was 8.5% in 2001 and 9.5% in 2002.**

| **Defense Contractor** | **Operating Margins** | |
|---|---|---|
| | **2001** | **2002** |
| Boeing | | |
| company | 6.7% | 7.2% |
| military | 10.8% | 11.8% |
| General Dynamics | | |
| company | 12.9% | 11.4% |
| marine systems | 8.6% | 7.9% |
| info systems | 9.3% | 11.8% |
| combat systems | 10.8% | 11.1% |
| L-3 Communications | 4.4% | 9.9% |
| Lockheed Margin | | |
| company | 3.7% | 8.5% |
| systems integration | 9.3% | 9.9% |
| aeronautical systems | 7.8% | 6.9% |
| Northrop Grumman | | |
| company | 7.4% | 8.1% |
| electronic systems | 7.6% | 8.1% |
| ships | 1.0% | 6.5% |
| integrated systems | 8.6% | 10.1% |
| Ratheon | | |
| company | 12.0% | 11.4% |
| electronic systems | 13.7% | 13.5% |
| C3l systems | 10.5% | 10.0% |
| Rockwell Collins | | |
| company | 16.3% | 14.7% |
| Teledyne | | |
| Company | 4.9% | 5.6% |
| **Average** | **8.5%** | **9.6%** |

**The operating margin for the successful biotechnology companies listed below was 31.8% in 2001 and 28% in 2002. This operating margin is 3.74 times and 2.91 times as great for 2001 and 2002 respectively as the operating margin for the defense contractors listed above.**

| **U.S. Biotechnology** | **Operating Margins** | |
|---|---|---|
| | **2001** | **2002** |
| Amgen | 44.2% | 41.8% |
| Biogen | 34.5% | 26.3% |
| Cephalon | | 25.9% |
| Chiron | 19.5% | 24.3% |
| Genentech | 22.7% | 24% |
| Genzyme | 22.3% | 21.8% |
| Gilead | | 17.4% |
| IDEC | 48.1% | 52.9% |
| MedImmune | 31.1% | 17.2% |
| **Average** | **31.8%** | **28.0%** |

**The operating margin for the successful pharmaceutical companies listed below was 29.5% in 2001 and 26.5% in 2002. This operating margin is 3.47 and 2.76 times as great for 2001 and 2002 respectively as the operating margin for the defense contractors listed above.**

| **U.S. Pharma** | **Operating Margins** | |
|---|---|---|
| | **2001** | **2002** |
| Bristol-Myers | 33.2% | 21.9% |
| Eli Lilly | 32.3% | 29.5% |
| Merck | 21.0% | 19.0% |
| Pfizer | 34.2% | 36.1% |
| Schering Plough | 30.0% | 27.7% |
| Wyeth | 26.1% | 24.5% |
| **Average** | **29.5%** | **26.5%** |

Operating margin is profit before tax. The operating margin for the defense contractors has been adjusted for good will. Operating margin is calculated by dividing a company's operating profit by net sales. It is also known as operating profit margin or net profit margin. Operating profit it typically assessed before taking into account interest and taxes.

Compiled from publicly available information with assistance from Michael King, Banc of America Securities LLC.

# Interview—Serguei Popov
# Journal of Homeland Security (November 13, 2000)

**Serguei Popov is a former scientist in the Russian biological warfare program. After obtaining a degree in biochemistry, he served as a division head in Vector and Obolensk, branches of the Soviet program dedicated to developing genetically enhanced bioweapons. His position allowed him to expand his research into the fields of molecular biology and microbiology. Dr. Popov worked at Vector from 1976 to 1986, then at Obolensk until 1992, when he defected to Britain and later traveled to the United States. He now works for Hadron, Inc., in microbiology and pharmacology.**

***Homeland Defense:*** *How did you first become involved in the Soviets' biological warfare program?*

**Serguei Popov:** I found work by speaking to Lev Sandakchiev, who later became in charge of Vector Institute. Lev wasn't my friend but I knew him very well. My wife was a student of his at that time, so there was a close connection. Of course, I had no knowledge of what specific programs they had decided to run, but in 1975, Sandakchiev wanted me very much to join his institute. And shortly thereafter I became a scientist for him at Vector.

***Homeland Defense:*** *What were some of your earliest projects at Vector?*

**Serguei Popov:** With my background in biochemistry and nucleic acid chemistry, I primarily studied DNA. At that time, it was not a very advanced science, but it was exciting and we tried to create artificial DNA fragments and artificial genes. That was my goal, actually, for the next several years, to make artificial genes. I eventually became the head of a department, with about 50-60 people working with me, half of whom were researchers.

Our approaches were straightforward, using mainly chemical synthesis. It was certainly easier than other available procedures. And chemical synthesis was attractive because it promised to do whatever we wanted. And of course Sandakchiev was interested. That same year, 1976, I became a department head—a department whose whole purpose was to learn how to design artificial genes.

***Homeland Defense:*** *Could you describe the different levels of security in your program?*

**Serguei Popov:** Early on, I was already at security level three, but there were at least four levels of security. At level one, the explanation, called "an open legend," was that there was no biological weapons program at all. The work at the institute was completely academic and open. At level two, there was "a closed legend" explaining that there was a strictly defensive weapons program. At the third level, a particular person was provided with a description of some programs there were and what were the true purposes of these programs. But even this wasn't the complete truth. The real truth was at level four, which I viewed only briefly much later on. I read these types of documents on only one occasion.

Level number four described the purpose of specific programs and their interconnections. I read some of them, but I didn't know the whole picture. And I believe that below level four, there was yet another level with a full description of all the bioweapons programs. That was for the government. I didn't have that big picture. I think that Ken Alibek had that big vision. I have just fragments of that vision.

***Homeland Defense:*** *When did you realize you were involved in biological weapons production?*

**Serguei Popov:** It happened both gradually and immediately. With a program like Vector, you know something is going on, but no one tells you what you are going to do, or what the precise purpose of your program is. People get involved step by step, in such a way that there is no way back. You sign papers, and you commit yourself.

***Homeland Defense:*** *How did the conditions at Vector compare to the working conditions in Biopreparat?*

**Serguei Popov:** There were subtle differences between the Siberian institution of Vector and the other institutions of Biopreparat. Lev Sandakchiev was a pure scientist and had never been involved previously in biological weapons programs. So, the approach of Vector was the scientific approach. In contrast, the people who organized the Obolensk Institute had experience in biological weapons. The whole mentality was different. In Siberia, there was more a sense of freedom, adventure, excitement, and a sense of discovery. The other place, as I understand it, was much more depressing.

***Homeland Defense:*** *At that time, did they tell you the United States was involved in offensive biological weapons?*

**Serguei Popov:** Yes, they did. They always did. And there was no way to explore that point of view, even if we believed otherwise. It was an official statement and no one doubted it.

***Homeland Defense:*** *Did they also tell you the United States was working on genetically enhanced weapons?*

**Serguei Popov:** That wasn't difficult to believe either. The United States is the biggest country, with some of the best scientists, you know. So I had no doubts.

***Homeland Defense:*** *So when did you realize the U.S. was out of the biological warfare program?*

**Serguei Popov:** Not until I came to this country. I knew what was written about the U.S. program. But I had a suspicion that nothing was happening in this country when I visited England in 1979. When I visited England, it didn't take long to pick it up.

***Homeland Defense:*** *Dr. Popov, this interview in generally targeted for the benefit of two groups: individuals with strong scientific background, and at the opposite end of the spectrum, policy makers with little background in the sciences but strong interests in the subject matter. But there is likely one question in particular that both sides could agree on in terms of importance. In our discussions with Dr. Alibek, agents like plague, anthrax and smallpox all sounded like very effective weapons.*

**Serguei Popov:** Oh, they are.

***Homeland Defense:*** *What then was the purpose of taking this next step, which was really leading-edge science? Why genetic engineering?*

**Serguei Popov:** The answer changed over time. Originally, the Soviet military wanted Vector and Obolensk to produce genetically engineered weapons because they wanted classical agents with new properties like higher pathogenicity and unusual symptoms. And ultimately, we did develop improved classical weapons, with new, unusual properties and resistance to antibiotics.

But it proved to be an illogical way to construct a weapon. There was a belief that new weapons, completely new weapons, without known protection and with new properties, could be superior. The classical agents were there, and they were effective, but initially the military wanted even more effective [ones].

***Homeland Defense:*** *Now, Dr. Alibek told us last month about how Biopreparat developed plague that was resistant to our ten most common antibiotics. They couldn't find a strain of plague resistant to ten, so they took one strain, made it resistant to five, and another to another five. Were you just looking for more effective ways to achieve the same result?*

**Serguei Popov:** Not exactly. When we talk about the whole program of genetically engineered weapons, it was a combination of several projects. For example, projects like "Bonfire" were specifically aimed at developing antibiotically resistant strains.
But there was a much bigger program, called "Factor." It was a program to create strains with the ability to produce certain biologically active substances as new pathogenic factors. It was not about an improvement of what was generally known. But the final goal of Factor was to create strains with completely new properties.

***Homeland Defense:*** *Did Factor also work with the classical agents?*

**Serguei Popov:** Yes. The initial vision was that the old classical biological weapons would acquire new, unusual properties so that, for example, prophylaxis would be difficult. Project goals included high virulence, high stability, and surprising new outcomes for the disease in order to confuse treatment. To achieve those goals, there were several directions. The first was to express short biologically active peptides. Then there was an attempt to introduce toxin genes into those strains. The toxin genes could be short peptide toxins or they could be proteins.

***Homeland Defense:*** *In follow-up, you commented on the plague issue, that somehow there was recent success in achieving the properties. Is that what you're suggesting?*

**Serguei Popov:** Yes. I know at least two examples of plague and smallpox strains which acquired new properties.

***Homeland Defense:*** *And what would those properties be?*

**Serguei Popov:** A gene responsible for hemorrhage formation was included in one viral strain and diphtheria toxin gene in another bacterial strain. Later, the Obolensk Institute published their results on anthrax with hemolysin gene. That was the third example. But again, in [the] case of diphtheria toxin, we were more interested in the outcome. The idea was that the vaccine directed against plague would not be effective. When we talked about those problems, there is no clear way to achieve those goals. That's why the programs constantly changed. The final purpose was the same but the way to achieve success varied.

***Homeland Defense:*** *For the benefit of the non-scientific audience, could you describe what a peptide basically is?*

**Serguei Popov:** A peptide is a short protein fragment. Peptides are of the same origin and display properties of proteins. But peptides are more direct in their action and properties. They may target specific functions. We have an example of small peptides like endorphins or enkephalins. Those peptides are approximately 30 amino acids long, and it is about 10 to 20 times [fewer] amino acids than in an average protein. The peptides can interact with a receptor, and they could be produced in a biological way. It's difficult to produce morphine or other drugs through genetic means. But endorphin peptides have similar properties. In the case of peptides, you make a very small DNA chain that codes for the peptide, and you introduce that gene into the genome of any agent. That's, in general, all you need.
Small peptides that are neuro-active were capable of changing behavior. Some peptides also created changes of behavior and could have other activities, because they were multifunctional peptides. One example of this was vasopressin, which affects blood pressure. Some peptides were toxins, while others offered a completely new approach for causing autoimmune diseases.

***Homeland Defense:*** *What do you think about press reports which suggest it's possible to take the toxin from cobra venom and splice it into strains of influenza?*

**Serguei Popov:** Those are all an exaggeration, but the idea is correct. I would doubt that cobra venom would be good for biological expression. Toxins must meet numerous specific requirements. But the simplest is that they should be easy to reproduce in biologically active ways. Many toxins are also big molecules, requiring energy and specific biological machinery to build and deliver them to their specific targets. If you

consider the simplest toxin, it should be short, it should not be sensitive to the environment, and it should be stable when created inside the body.

***Homeland Defense:*** *Did you have any success in creating these?*

**Serguei Popov:** Well, essentially, yes. There are several toxins which are very effective, like peptide toxins from cone snails (conotoxins). However, there were some problems. One of them was that those toxins required two specific cystine bridges. Without those bridges they weren't biologically active, and that was a complication.

***Homeland Defense:*** *But you successfully produced those toxins?*

**Serguei Popov:** Finally, yes. The work on inserting them into smallpox virus continued till the program was terminated.

***Homeland Defense:*** *Was it your goal to produce the toxins in quantities sufficient by themselves, or was it always part of your plan for one organism to produce the toxins inside the host?*

**Serguei Popov:** The final goal of Factor was to create microorganisms that produce these toxins inside the host. But there was another program that dealt directly with toxins themselves. It was closely linked to Factor because when we studied the action of toxins engineered into microbes, we had to know their behavior, meaning we needed them in control experiments. The goal of genetically engineering the weapons was to create strains of microorganism producing toxins, such as viruses coding for toxins and ultimately producing toxins.

***Homeland Defense:*** *Were you successful? You were talking about genetically engineering strains of the classic biological weapons, so that they were more effective, had different properties, and presented themselves in new, challenging ways. But did you ultimately produce an anthrax or smallpox agent with new properties?*

**Serguei Popov:** Yes; for example, plague with diphtheria toxin has been produced. But the whole program was a difficult task. Some approaches proved to be more successful than others. One tactic, immune mimicry, was to induce an immune response against myelin (found in the body's nervous system). Because the cloned myelin protein (or its fragment) would be very close in structure to the body's, host responses against the infection would be directed against the body's own myelin. As a general principle it's been discussed for many years, but it's a very difficult practical task to pull off. Damaged myelin interferes with the transmission from the brain to the peripheral nerves. Most likely its destruction by a microbial agent would induce paralysis and death.
For example: You get the flu, and then you get a complication from the flu. In that case, the immune system, which struggled with flu virus, could target your body as well as flu. When your body tries to heal itself, it actually does the reverse.
In Obolensk, we did extensive experimentation with different bacteria carrying a myelin gene. We finally found that an agent called Legionella created very strong immunological

responses. The myelin peptide it produced was very immunogenic because the immune system was activated by the infectious process. That's what resulted in paralysis and death of infected experimental animals. And what is important as well, a lethal dose was much lower, only a few Legionella cells.

***Homeland Defense:*** *Were you able to do that in animal models, like primates?*

**Serguei Popov:** No, just guinea pigs. We were initially ordered to do it, and we did not expect any technical difficulty, but the program had been abruptly stopped at the level of primates.

***Homeland Defense:*** *And how long would it take before the target was affected?*

**Serguei Popov:** Essentially, it's two weeks.

***Homeland Defense:*** *And there would be no symptoms before that?*

**Serguei Popov:** No, there wouldn't, and there would be no agent in your body. It will be completely clear.

***Homeland Defense:*** *Doctor Popov, this sounds like a topic that very few people in the areas of biological warfare and homeland defense have discussed. It also sounds like a very challenging weapon to guard against. Could you offer any additional explanations on this subject?*

**Serguei Popov:** Certainly. In general, there is a basic technique to make a viral or bacterial genome easier to manipulate genetically. First you take a gene of interest and you put it in a suitable biological vehicle, often called a vector. Here the gene can be changed, and new properties can be added. More importantly, the vector could be introduced into a bacterial strain, so that the bacteria will carry it, and will acquire the properties to produce the substance the gene codes for. Usually, the bacterial host is harmless, but it can be pathogenic. The gene product can be pathogenic as well. In the above case of the myelin peptide, [the] immune system eliminates the bacteria that produced it, but the peptide triggers a slow destructive immune response. And you are right when you say people in biodefense have never considered this approach.
Let me provide you with another example of a new bioweapon idea, which was under development when I left Russia. Imagine plague carrying a whole copy of a virus. You would expect that people infected with genetically engineered strains of plague would be treated for plague. But the antibiotic treatment would actually make the patient worse because of the antibiotic-induced release of the virus from its copy. A virus infection on top of a bacterial infection may be a situation you will never be able to properly deal with.

***Homeland Defense:*** *So you don't have the virus until you kill the bacteria?*

**Serguei Popov:** No, you don't.

***Homeland Defense:*** *In the exercise we did in May, called "Topoff," in Denver, we did the simulation of a plague attack, and they chose plague because treatment, in theory, is simple. You just need to provide people with antibiotics. But in your scenario, it wouldn't matter. No matter how effective we are at controlling it, the more antibiotics you pass out, the more viruses you release?*

**Serguei Popov:** Exactly. Each disease has completely different symptoms and incubation periods, which means treated people will appear healthy and think they are fine. But the treated people are still sick. They simply don't know it. And a new viral disease can appear after a few days in cases of recombinant plague, or two or three weeks in case of recombinant Legionella. People will experience paralysis, and their central nervous system will cease to function.

***Homeland Defense:*** *And how long does it take for this paralysis to take effect?*

**Serguei Popov:** It's difficult to say, but the disease itself in animals is quite fast (a few days).

***Homeland Defense:*** *Some of the peptides you've mentioned are extremely novel. But in looking at some of your viral agents, was it more in your interest to create new properties, or to perpetuate existing systems?*

**Serguei Popov:** Initially, the purpose was to bring new properties to existing strains. But the whole program shifted development in the 1980s into new strains. We struggled with the problem of small peptides creating new properties, putting them into active strains. We began to ask ourselves, "Why should we insert peptides into classical strains when we could put them in new strains with new properties, and it could become a weapon even more difficult to deal with or cure?" So the whole plan of the program was shifted to making new virulent strains. In this area, I was relatively successful in making autoimmune peptides effective.

***Homeland Defense:*** *Was your specialty in bacterial vectors, or did you look at viral vectors?*

**Serguei Popov:** I studied viral vectors originally. But after I was transferred to the Obolensk Institution, I worked on bacterial vectors as well.

***Homeland Defense:*** *You stated earlier that one of the goals of Project Bonfire was vaccine resistance. How much success did your program have in developing a strain of anthrax resistant to vaccinations?*

**Serguei Popov:** I heard a story in 1986 about developing an anthrax resistant strain expressing hemolysin, but [at] that time it wasn't considered a very productive way of doing vaccine resistance against anthrax, and that was in place a long time ago. I did not think they would find anything very exciting about this. Surprisingly, it finally worked.

***Homeland Defense:*** *Out of curiosity, was tularemia an interest of your program?*

**Serguei Popov:** Well it was, but it was considered an old workhorse, an old vehicle. In terms of genetic engineering with tularemia, there was little activity.

***Homeland Defense:*** *How about mycoplasm?*

**Serguei Popov:** We didn't try that. I know that they looked at it, but that was in a different institute.

***Homeland Defense:*** *Did your program share work with allied countries, or was it only with Russian scientists?*

**Serguei Popov:** No, my program only employed Russians. And there was no change in this policy up until 1992, when I left Russia.

***Homeland Defense:*** *So you did no work except for biological weapons work?*

**Serguei Popov:** Yes, but it was not easy to distinguish between pure science and military science applications. In a way, everything had military usage. Anything considered "pure science" was questionable. Take an example of a recombinant interferon project I was in charge of at Vector. It was believed to be a potent antiviral drug for troops' protection.

***Homeland Defense:*** *How much control did the Soviet Union have over your life? Was your travel restricted?*

**Serguei Popov:** Traveling abroad was completely impossible. I managed it once and that was it. But travel inside the country was restricted in terms of procedures. You had to be back in the lab by certain times. That type of thing took place frequently.

***Homeland Defense:*** *When you began this in the 1970s and 1980s, you were involved in what we would call leading-edge technologies. Only Russia, the United States, and maybe a few other countries like the United Kingdom could reasonably succeed in this area. Because of the biotechnology revolution, do you think this type of research is continuing today in other countries like Iran, China, India, or North Korea?*

**Serguei Popov:** I think the answer to your question is: no doubt. But the knowledge is not there, I hope. Creating biological agents is not only technology and procedures. But the most important thing is what to do, and how to achieve success.

***Homeland Defense:*** *Do you believe it's possible some of these countries have recruited former colleagues of yours to work for them in this area?*

**Serguei Popov:** Oh, I'm pretty sure they did.

***Homeland Defense:*** *And how many people worked in your program at Vector, at your level and with your expertise?*
**Serguei Popov:** It's hard to estimate. I know there were several institutions, with several labs in each. There were probably a few thousand researchers. But at my level, there were maybe several dozen, as of 1992.

***Homeland Defense:*** *Russia has ostensibly been opened to travel, but we assume someone with your skills would probably have been discouraged from leaving. Can you tell us about how you came out?*

**Serguei Popov:** Well, of course it wasn't the straight way. When I recognized that everything was collapsing and the KGB was having problems maintaining control, I decided it was a good time to get out. My problem, however, was that I had no money at all, not even to buy food. My only connection outside Russia was in England. I had visited England once in 1979 and I had some good friends over there in the scientific community. In fact, that's why [the] Soviets didn't let me join the communist party in the Soviet Union.
So I wrote those friends by sending them email and faxes. Finally, they found some money for me to conduct research, but still didn't have money for tickets. At the time, I only had four dollars in my pocket.
But the Royal Society promised to pay me in England. So I negotiated a short-term pass to England, and the KGB agreed to let me go. They may have agreed because they wanted the money that would come from the science I promised them. So they let me go. I just didn't go back.

***Homeland Defense:*** *Do you feel like you've been threatened since then? Did they follow you?*

**Serguei Popov:** They followed my wife. When I left my home, I had to leave my family and my children in the Soviet Union for about a year. She knew I was going. But that was the only way to earn money, so that we could purchase their passports.

***Homeland Defense:*** *When you left, were you debriefed by British or American intelligence services?*

**Serguei Popov:** Nobody was interested. Not a single person. Only much later, in Dallas, Texas, was I debriefed.

***Homeland Defense:*** *So where have you been working and what have you been doing since you left Russia in 1992?*

**Serguei Popov:** Well, first I came to England. The Medical Research Council arranged for me to study molecular biology in Cambridge, and I studied HIV virus for six months there. Then I traveled to Dallas, and I researched microbiology and pharmacology. And today I work for Hadron.

***Homeland Defense:*** *So to the best of your knowledge, the genetically engineered agents were not weaponized by the military?*

**Serguei Popov:** That is correct, but with a few exceptions. I think plague with diphtheria toxin was weaponized. That's my impression. The antibiotic-resistant strains of plague and anthrax were also weaponized. But as far as the Factor program is concerned, not very much was weaponized. I also know that hemorrhage gene was introduced into smallpox virus; I don't know the final results.

***Homeland Defense:*** *Did you work on the smallpox virus yourself?*

**Serguei Popov:** Yes. But that project belonged primarily to another person. And I don't know if they decided to continue this work.

***Homeland Defense:*** *There have been rumors of combining smallpox and Ebola after some fashion. Some have suggested making an agent as contagious as smallpox and as deadly [as] Ebola. Is such a thing possible?*

**Serguei Popov:** This idea could be accomplished on a genetically defined level, or by simply combining both. The physical combination was the subject of discussion. But not everybody liked it because of the difficulties involved.

***Homeland Defense:*** *Did you hear about this in Russia or after you came here?*

**Serguei Popov:** From 1986 I heard some rumors on these types of agents. Both bacterial and viral combinations were discussed, but I was not included in these talks. To be honest, I had little interest in this area.

***Homeland Defense:*** *You mentioned the development of "subtle agents," using biopeptides and bioregulators. Did Vector also work on similar agents that would affect people from a psychological perspective?*

**Serguei Popov:** Yes, endorphins, enkephalins, and other neuromodulating peptides. It has been discovered that personalities could be adjusted with these agents. For example, you could make people more aggressive. Or you could create feelings of insomnia, where people wanted to sleep, but would never feel tired.

***Homeland Defense:*** *In your program, who decided where the work would go? Was it the military, the government, or the scientists?*

**Serguei Popov:** Factor was literally created overnight in a Moscow kitchen by some military officers, sometime around 1978. From that point on, it became an official program, but they always took feedback from scientists. They realized it was the perfect way to make new agents, which could be essentially undetectable, and furthermore could get around the biological weapons treaty. Many of the agents created by Factor would be very dangerous, but they would not be illegal.

**Editor's note:** *The Journal of Homeland Defense* disagrees with the Soviet claim that such activity was legal. The Biological and Toxin Weapons Convention prohibits any type of activity (development, production, or stockpiling) regarding the offensive use of biological or toxin weapons. Article I from the convention is provided at the end of the interview for the readers' perusal.

***Homeland Defense:*** *You've mentioned quite a few unsettling agents in today's discussion. But we want to be clear on this subject: were any of these agents weaponized in mass quantities?*

**Serguei Popov:** No, they were not. We ceased this work around 1991, after funding was cut.

***Homeland Defense:*** *What happened to the research related to these projects?*

**Serguei Popov:** Everything was archived and put into storage, and I believe it is still there.

***Homeland Defense:*** *This information sounds sensitive, if not dangerous. Do you know if this data is currently secure?*

**Serguei Popov:** To the best of my knowledge the information is still safe.

***Homeland Defense:*** *What about your former colleagues? Do you believe any of this work you've discussed is still going on?*

**Serguei Popov:** Yeah, I'm pretty sure. I don't have any direct evidence. But recently I've begun looking up what my former colleagues have published. All I found were a few lousy, lousy papers. This suggests they are currently working on something they cannot publish. And that's a good indication the program is still functioning.

***Homeland Defense:*** *Those papers are just cover stories?*

**Serguei Popov:** Yes. That's all they are allowed to publish.

***Homeland Defense:*** *Finally, we should mention that this is your first public interview since you departed the Soviet Union. You said that the U.S. Intelligence Community debriefed you. Were the people who conducted this interview fully qualified to conduct your briefing? Did they have the proper scientific background to fully appreciate the nature of your previous work with the Soviet Union?*

**Serguei Popov:** No, they did not sound like scientists. However, I told them about the directions of my work in the Soviet Union. They were mainly concerned with the issues of possible terrorist attack using bioweapons.